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MEDICAL SOCIAL ASPECTS IN PRACTICE

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BOSTON

A considerable fraction of the successful care and treatment of patients and, undoubtedly, the prevention of much illness is to be identified with the proper consideration of sociologic factors. The case of every patient who consults a physician has a medical social aspect. This social component of medicine may vary widely in importance, but frequently it plays a major rôle in diagnosis, prognosis and treatment and in the prevention of disease and unhappiness. Every one is constantly confronted with social problems which he settles without great difficulty or to which he soon adjusts himself, but the problems may become of medical significance, so that, as Parry of Bath indicated late in the eighteenth century, it is often more important to know what kind of a patient has a disease than what disease the patient has. Lack of thoroughness and imperfect skill are causes of many errors in the prevention, diagnosis and prognosis of disease and in the treatment of patients. The diagnosis of the person is often neglected when the diagnosis of disease is considered in detail.

The medical social aspects of each case are intertwined intimately with the psychiatric, environmental, economic, hereditary and allied aspects. For centuries physicians have recognized the importance of such conditions in prescribing wisely for patients, yet seldom are physicians scholars of this subject. This problem is not new. James Jackson, the second Herseyian professor of the theory and practice of psychic at Harvard wrote in 1861, when he was 84 years old

Among the sciences, the principles of which it is necessary for the physician to understand is that of human nature, or, otherwise described, the principles of the philosophy of the human mind and heart. This strictly and properly is a branch of human physiology. It is, however, a branch which is ordinarily not brought into view. The mind has much to do with the health of the body.

He indicates clearly in his various publications the importance of studying and applying knowledge concerning all aspects of the patient's life.

Although the physician in private practice has often attempted to consider faulty character, undesirable community life, unwholesome

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard University Medical School

human relations and other aspects of the patient's self, knowledge concerning such subjects is not frequently obtained and applied. Certain of the more obvious medical social problems are, of course, usually considered, for example, financial complications, in advising a sojourn in Florida, or religious dietary restrictions, in advising food for persons of certain faiths. Able young physicians soon appreciate that social aspects form an important feature of many cases and thus they often wish that they knew more concerning patients as individuals. The general practitioner of many years ago acquired this sort of information with ease and utilized it most successfully. There is, of course, no dispute regarding the fact that many physicians with insight and ingenuity do attend admirably to the social aspects of their cases, but more organization and diffusion of knowledge concerning medical social problems, with the development of intelligent methods of study and the acquisition of more real knowledge, would be a great step in advance.

The character of medical practice today, with its division into specialties, and the many trends of modern times do not favor the doctor becoming intimately acquainted with his patient's personal life without conscious effort, as the physician of one hundred years ago did almost automatically. Today there is vastly more sound knowledge concerning the influence on health of living conditions and the problems of life, but living conditions have become much more complex with industrialization, urbanization, the results of invention and the development of many modern customs leading to haste and often to waste. Thus, the physician today needs not only to have such knowledge concerning social problems as was available to the physician of years ago, but he must have much more information of this sort and apply it thoroughly. The science dealing with the relation between human behavior and health is in its infancy, and the progressive physician should attempt to advance medical knowledge in this direction as much as he has advanced that concerning organic disease within the past quarter century.

The development of hospital social service, which is now wisely termed medical social work in hospitals, was begun particularly because of the necessity and desirability of the division of labor among the medical and allied staffs of hospitals. It became evident that in institutions lack of time, insufficient training or inability prevented the physician from carefully considering the social component of medicine in each case. Hospital social service has become a potent means for more accurate diagnosis, more effective treatment and the prevention of suffering, but it is effective directly in relation to the quality of the medical work. High grade medical work permits good social work, and vice versa. It has taken time for some physicians to realize that many failures in treatment at hospitals are due, in part, to elements outside the limits

of what might be called conventional medical practice, the same is, of course, true in private practice. The efforts of medical social workers devoting themselves to the study and understanding of social conditions and of physicians taking full charge of all aspects of the patient must be closely related. The physician must lead. The social worker contributes to the understanding of the personal and environmental factors in the health of patients, she may aid in carrying out treatment and help in many ways, but the physician must remain the chief, and the social worker must cooperate closely with his program. Intimate relations between the various clinics of a hospital are essential. The social clinic (social service department) improves the work of all the clinics and should be on the same plane as other clinics. Thus, the importance of social problems will be fully appreciated, and the patient will receive the greatest possible benefit.

The development of medical social work in hospitals during the past quarter century has been one important factor in bringing to the physician knowledge concerning the social component of medicine. It has helped to awaken him to the importance of these problems, which, perhaps, he tended to neglect during the era of rapid development of scientific medicine. The work of psychiatrists, educators and other persons interested in the problems of human welfare is also responsible for a better understanding of the vast variety of medical social problems with which the physician is confronted. Thus, whereas it was once recognized that a phase of medicine practiced by the good physician was lacking in institutional work, and hospital social service was developed largely to fill that need, the technic of social workers has become so perfected that not only a knowledge of their methods, but also the information which they hold, can aid physicians in seeking the social history and applying such knowledge in their private practice.

The physician in private practice at present rarely has recourse to an expert medical social worker, although he may call on medical specialists, such as the roentgenologist or the heart specialist, for aid. The physician himself must attend to the social aspects of his patient's case, although he may receive help if he knows how to seek it, especially from the psychiatrist, clergyman and the schoolmaster. Seldom has the physician received training in the subject, and he must learn for himself not only the significance of medical social problems but methods of studying them. He must become acquainted with community resources. He must learn how to teach persons the most beneficial way of conducting certain careers and the business of actual living, which is to be distinguished from the preliminaries of living, such as education and the obtaining of shelter, food and other supplies. All such matters constantly confront persons for decisions. That art which lies

particularly in keeping the peace with those with whom one is thrown or with one's mental and physical environment must be taught in each case so as to be suitable for the given person. In other words, recognition must be given to the rhythm of life, not only to the factors that affect the ebb and flow, but also to the surging and conflicting currents. It is the study of such matters that leads the wise physician to success in treatment.

One can still find physicians who take the view that medical social work concerns only the poor and friendless. They forget that such work is not concerned with charity or spiritual welfare, as is that performed by the church. The social problems in private practice are as numerous and frequent as in hospital practice and are often more complex and difficult to correct. This is because the higher the social order of the patient, the more complicated the social issues and intricacies of life are apt to become. To appreciate this, one only has to think of the greater complexities arising in the life of a person with servants, children in private schools, many friends and multiple social, professional and business obligations, as contrasted with the life of a day laborer, yet both may be confronted with basically the same medical social problems.

REPORT OF CASES

The following three cases, presented in outline, illustrate the importance of the social component of medicine in practice. The first case illustrates the failure of that prescription of great therapeutic importance, rest, because of lack of complete understanding of the patient, and then illustrates the success obtained with this prescription after the social aspects were known and the knowledge was applied.

CASE 1—Mrs. A, 44 years of age, the wife of the president of a large industrial corporation, had mild atrophic (rheumatoid) arthritis of five years' duration. Among other therapeutic measures, rest seemed important. She admitted that she always felt tired, but insisted that she did nothing to get tired. She recognized that she had many duties to perform in relation to the care of her two daughters, her relatives, the management of her house and suburban estate and charitable and social organizations, but she said, "They are pleasant matters to attend to, and surely they cannot be the cause of fatigue." Her physician, who had seen her only in his office, without any further information about her daily life, the nature of her home or her attitude toward people or affairs, said to her, "You must rest an hour each morning and afternoon." Time passed, and she was no better. Another physician called into consultation believed that rest, in the complete sense of the word, was essential, and that although the patient had lain down two hours a day she had secured little rest. He visited her home, he observed its character, the patient's behavior and the behavior of the people with whom she came in contact daily. A few salient facts from among the many obtained were as follows. The only time the house was quiet enough for her to write personal letters was late in the evening. Mrs. A admitted that she feared that her social prestige

would be diminished if her correspondence was not voluminous. She often had breakfast with her husband at 7 30 a m, for it was only at breakfast that he had time to give her directions about their handsome estate, of which they were proud and which they wished to keep in splendid condition. Many days in the week she gave directions to the gardener and took pains to see that the work was properly completed. "But," she said, "I never have time to be thorough about these matters, I crave time to read about them, but that would be selfish."

Mr A was physically strong and led an intensive business life. He often brought home business guests for dinner on a moment's notice, and was anxious to entertain socially at frequent intervals. He was never tired and did not at first understand why his wife should feel fatigued. He expected her to supervise and help in a meticulous way in many matters of mutual interest and to send many telegrams and messages concerning business. She was often called to the telephone fifteen times a day. At the beginning of the day she was apt to hurry to complete the household duties and became irritated when there was delay. She usually had an appointment away from home soon after 9 o'clock. Eight committees demanded her presence. She got along well with the members of all except one—the one which she considered the most important and which met frequently. On this committee were the wives of her husband's business associates and also of his competitors. As chairman, she could not do what seemed wise for fear of causing unpleasant situations which would reflect on her husband's business.

Her two daughters, aged 18 and 16 years, respectively, caused anxiety. The elder presented a peculiar behavior problem. Mrs A said that she "just failed to understand her and the more she tried to help the worse the child behaved." The younger daughter was thin and ate an improper diet largely because she "must be slim." At meals Mrs A always antagonized this child, which, in turn, often led Mrs A to have transient emotional outbursts. She believed that she enjoyed luncheon parties and "knew she simply must attend many of them." Her mother-in-law lived in an annex to the house with her own retinue. She was 85 years of age and had senile dementia. Mrs A felt obliged to see her daily, for her husband's sake, and to see that her servants performed their duties properly.

The rests which Mrs A had taken consisted of lying down for a total of about two hours a day with the telephone beside her couch, which she answered when the bell rang. During these "rests" she made memoranda with pencil and sometimes talked with people she "had to see." An endless array of simple problems concerning servants, friends, charities, horticulture and other matters were disclosed. Mrs A believed that she never could say "No" to requests or invitations, as that would be selfish, and her husband wanted her to be prominent and to accept every opportunity for social contact. She recognized that she attended to many matters, but believed that she was not capable of completing anything worth while.

Conversation with Mr A showed that at heart he was sympathetic. He said that he had simply never stopped to think "what he was asking of her." He agreed to help arrange matters so that she could obtain true rest, tranquillity with relaxation, the minimum of psychic trauma and an opportunity to lead a well planned life. The physiologic mechanism of chronic fatigue and the influence of fatigue and rest on the functions of the body were described so that both Mr and Mrs A fully appreciated the reasons for, and the importance of, rest for Mrs A. This conversation made them cooperative at once. They were highly intelligent and fundamentally sensible persons. Arrangements were made so that Mrs A spoke over the telephone only at definite times each day. Mr A saw

to it that none of his business matters were handled by his wife, although he made it a point to keep her in as close touch with such affairs as before. She agreed to resign from certain committees and was easily persuaded to recognize that careful attention to a few matters would be more likely to lead to accomplishment than a diversification of efforts. Arrangements were made for certain household matters which she had formerly supervised to be attended to by a servant. She was instructed to answer practically no invitations verbally, thus making it possible for her to reflect and to answer more easily and more often in the negative. She was taught how to start the day slowly.

She agreed not to discuss the behavior of her daughters with them for eight weeks. With a physician's assistance, which included advice to Mrs. A., both children soon improved, much to the happiness of the family. These and other matters were adjusted to the delight of all members of the family, with resulting improvement in the health of each. Mrs. A. then had a calm life, she truly rested attempting to sleep one hour each afternoon. She was taught how to relax all the muscles of her body and was instructed to practice this several times each day. Soon she found that she had time to enjoy the beautiful garden and realized that previously it had been more of a drudgery than a pleasure. "Employment is nature's best physician," Galen wrote, "and essential to human happiness." Mrs. A. had ample employment, yet learned to carry out her activities with much greater tranquillity than before. She admitted that she accomplished more in a thorough manner under her new regime. Her daily life was changed from one of intensity and often relatively useless activity, with frequent irritability, to one of happiness for herself and her family. Not only was she improved much in all ways, but as a result of her improvement her children are better and her husband is happier, indeed, all of them are enjoying life more than before.

The course of events outlined permitted Mrs. A. to obtain much more rest without lying down for a longer period. This was accomplished only after prolonged study of the social factors and after many conversations with the patient and her family and friends. The physician must appreciate that in order to unravel such problems as that presented in Mrs. A.'s case, and to succeed in accomplishing the object desired, a large amount of work is necessary. Treatment consisted of much more than simply saying, "Rest." It necessitated an appreciation of the sociologic factors, an understanding of her home from inspection and the cooperation of her husband and children in particular.

Physicians probably often neglect to recognize that failure in treatment may be due to them rather than to the prescriptions which they give the patient. Lack of imagination and scientific curiosity may often be the cause of their failure. Unfortunately, physicians sometimes indicate that they have no time or patience to attend to the needs of nervous people, that these problems bore them and that such disorders as chronic arthritis are uninteresting. That attitude is unfortunate, the physician should be deeply interested in his patient or else not accept him for care. Therapeutic success depends on treatment carried out thoroughly, intensively and whole-heartedly, with attention to all the aspects of the case. The physician should show a deep interest in

human beings and in their economic and social structure, as well as in their physical and psychic state. The value and importance of such work as the adjustment of Mrs. A's life sometimes passes unrecognized, yet does more dramatic work, such as an extensive surgical operation, accomplish more?

In evaluating medical social aspects, it is important not to interpret them in terms of what the physician, personally, would do or like, or in the light of his own life or that of his relatives. Happiness can exist in circumstances that to him may seem intolerable. He must not be prejudiced, and he must have a wide breadth of vision. There is, perhaps, nothing more difficult than to decide wisely what is best for other persons as concerns the art, business and preliminaries of living.

The problem of being beset with the cares of living so that one has no time for life itself is common. The present century is one of restlessness, there is a continuous mood of excitement. Many people have not the least idea why they are in a hurry all day long. One may observe persons of the leisure class rushing through streets, crowding out of trains and the like, as if the most serious and urgent tasks were awaiting them at home. They simply yield to the general movement of the times. This type of problem is one that concerns the medical social aspects of many cases as, for example, the case of Mr. Y.

CASE 2—Mr. Y, a quick-tempered person with duodenal ulcer, had become repeatedly symptom-free after rest in the hospital and a proper diet. The factory which he supervised had been run satisfactorily. Apparently, his affairs were in good order, and he appeared happy. However, when he was at work the symptoms of duodenal ulcer always returned. The social aspects of his case were at last investigated. His daily life was one of incessant haste, he interviewed certain persons repeatedly because he never remembered to complete his object at one time, and his methods of work were found to be badly organized—papers were constantly mislaid, and he permitted his work to be interrupted unnecessarily. Furthermore, he attended to matters which he admitted did not concern his job, because he used to attend to them years before when he was a foreman in the factory, and his tendency was to run slowly, rather than to walk, as he went from place to place in the factory. He had no hobbies or interests outside of his work, and his home was barren of books and pictures. Each night he worked on problems relating to the factory, never considering his children, and rarely did they or his wife do anything together except eat meals, at which business was the chief topic of conversation.

It seemed that if this state of affairs could be corrected and if the patient could have carefully explained to him the influence of emotions on the digestive organs and functions of the body, as has been so well set forth by Cannon, a start would be made in the prevention of the recurrence of his symptoms. He was taught how to banish from life all superfluities and thus was schooled in the art of having time. The means of escape from his ineffective haste was the resolution not to be swept away by the prevailing current of the age, as though he could not have a will of his own. The habit of systematized work, a preservative of physical and intellectual health, together with regular exercise and brief

periods of rest, was instituted. After a year he was better, but whereas he formerly appeared happy, he now seemed unhappy. The character of his life was studied further. It was learned that for years he had believed that he was not wanted in the social community in which he lived because he had "risen from the ranks," while his neighbors had largely inherited considerable money. This idea was found to be chiefly of his own creation. As time passed, he was urged to accept the invitations of his neighbors and to join in their social life. This was accomplished particularly by the physician explaining the situation to two of the patient's friends, who were most helpful. Within another year he took time for relaxation and exercise with his friends and became much happier. At home his horizon broadened. He continued with the rearrangements regarding his work and increased his social activities, coincidentally with this, the symptoms relating to the ulcer have been slight for two years. Mr. Y. learned much about the art of work, the art of having time and how to fight the battles of life, as the result of the assistance which a physician gave him after a careful study of the medical social aspects of his case.

The able physician must be alert for opportunities to practice preventive medicine. The prevention of unsocial states can lead to an untold amount of good. The following case illustrates how preventable social conditions lead to illness and how important it is for the physician to consider the family as a whole when taking care of one member.

CASE 3—It was decided that the patient, a 16 year old girl with incipient pulmonary tuberculosis, should be cared for at home. She had devoted parents with, apparently, a good income and two brothers, aged 12 and 14 years, respectively. Their home was neat and contained choice books, nice pieces of china and antique furniture. A glassed-in piazza was built for the benefit of the patient. The two boys were not examined for tuberculosis because, according to their mother, "it did not seem necessary." The mother soon found that she had no time to give to the younger children. Everything was done for the sick girl. She was given expensive food and every attention. The father became anxious and attended to intricate details regarding his daughter. Soon much conversation about expenses arose, a servant was released, the boys heard discussions about economy and learned that nothing could be spared from their sister's needs. The father took on some extra literary work, cut his rest hours and became fatigued and more anxious about finances. Both boys began to receive much lower marks at school than formerly, the elder lost weight, and both appeared tired. The schoolmaster brought this state of affairs to the parents' attention. Examination of the boys revealed no tuberculosis. Another physician was consulted, who confirmed the absence of this disease. However, he learned that the boys had been anxious about their sister for months. They had never had the situation explained to them and expected her to die. They told how they had heard so much about economy that they thought that they could help if they went without their mid-morning lunch at school and ate sparingly at home. The boys felt that they were neglected and longed to have their mother read to them as she had done before their sister was sick. The parents admitted that they were so wrapped up in their daughter's interests that they had neglected to "even think of their sons." The boys had often spent hours at night talking about their sister and wondering how they could help. They believed that their family had lost so much money that they soon

would all be in the almshouse. They obviously became unhappy and suffered from mental anxiety. They even believed that their parents had stopped loving them, and yet they strove to think in what way they could help.

The facts were explained to the boys. Their sister was recovering rapidly, the parents did not have as much money as formerly, but it was extremely unlikely that they would be obliged to change their mode of living in a fundamental way. The mother and father were greatly distressed when they realized how little attention they had given their sons and were deeply touched by the motive of their thoughts. They arranged to give the boys more personal attention and saw to it that they had a proper amount of food. Soon the whole family was happy, the boys gained weight and again did well in their lessons, and before long their sister's tuberculosis was completely arrested.

The psychology of children is an important and large problem and will not be discussed in this article. It is a mistake to make mysteries of illnesses, it is usually wise to inform all members of the household of the facts about a case. One may also note that discussions before children regarding financial depression, family income and the like are apt to be interpreted by them as more serious than the facts demand. Anxiety over financial problems is, of course, common and can lead to many types of medical social problems. Even when reduction of the budget is great, a clear appreciation of the facts, with a wise selection for expenditure, together with an adjusted view of life, can permit happy lives to be led in spite of economic distress.

COMMENT

The matters which I have discussed seem simple, but it may require considerable experience and often much time to obtain medical social information and apply it usefully. Tact and personality play an important rôle, but an acquaintance with the stream of world thought and the actions of human beings, an understanding of "the conflicts of principle," "the meaning of right and wrong" and much other information of this sort are valuable when treating patients whole-heartedly and intensively. As has been noted, the ancients and the physicians in general practice of years ago developed knowledge of the medical social aspects of medicine, and medical social workers in recent times have been responsible for unfolding and clarifying such knowledge. Today there is the problem of how the young physician can obtain modern knowledge concerning the social component of medicine. This is a problem of medical education. It is being studied in a few medical schools where significant teaching of the subject is undertaken. Clinicians have the responsibility of teaching the social aspects of medicine. The need is to permeate the curriculum and to instruct the instructors in the subject. Time will be required to accomplish this. At present in a relatively few clinics special exercises illustrating the value and impor-

tance of medical social work are given. The generation of physicians now in their third decade of life will advance the present knowledge of human behavior and of the intricate effects of social, economic and allied disorders on health. They will be aided by professional medical social workers. An intelligent appreciation of these problems and an understanding of how to correct unsocial situations not only can save suffering, but can lead to the prevention of waste, useless efforts and unhappiness.

Many physicians with ability and insight have always attended to the medical social aspects of cases more or less well, but the important thing to recognize is that careful study and formulation and extension of knowledge in regard to these matters is needed, rather than leaving them to haphazard abilities or to individual interests. The field is a difficult one for reliable scientific study, because it involves all the complications of human life. Even so, physicians will gradually become more and more awakened to the increasing importance of social factors in medicine and will apply modern knowledge of this sort intuitively, not only in the hospital clinic, but also in private practice.

ETIOLOGY OF HODGKIN'S DISEASE

II SKIN REACTION TO AVIAN AND HUMAN TUBERCULIN PROTEINS IN HODGKIN'S DISEASE

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CHICAGO

The etiologic relationship of Hodgkin's disease (lymphogranulomatosis) and tuberculosis remains uncertain. Most of the investigations designed to solve this problem have been the experimental injection of diseased tissues into animals or cultural studies. Injections of "pure" Hodgkin's tissues do not regularly produce tuberculosis in animals, and cultures of the same tissues only occasionally yield a growth of acid-fast bacilli. The reports of L'Esperance¹ claiming that tissues histologically typical of Hodgkin's disease produced tuberculosis in chickens—an animal species not previously used for this purpose—gave a new impetus to such studies. Utz and Keatinge² stated that they had confirmatory evidence. Van Rooyen,³ Garrod,⁴ Stewart,⁵ Wallhauser⁶ and I⁷ failed to confirm the findings of L'Esperance.

Numerous early investigators of Hodgkin's disease performed tuberculin tests on some of their patients in an effort to obtain information on the relationship of the two diseases. As early as 1902 Reed⁸

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1 L'Esperance, E. Experimental Inoculation of Chickens with Hodgkin's Nodes, *J Immunol* **16** 37 (Jan) 1929, Study of a Case of Hodgkin's Disease in a Child, *ibid* **18** 127 (Feb) 1930, A Case of Pel Ebstein's Syndrome of Tuberculous Origin, *ibid* **18** 133 (Feb) 1930, Studies in Hodgkin's Disease, *Ann Surg* **93** 162 (Jan) 1931

2 Utz, L, and Keatinge, L. Hodgkin's Disease, *M J Australia* **1** 397 (April 4) 1931

3 Van Rooyen, C E. Aetiology of Hodgkin's Disease with Special Reference to B. Tuberculosis Avis, *Brit M J* **1** 50 (Jan 14) 1933

4 Garrod, L P, in Horder, T, and others. Rose Research on Lymphadenoma, Bristol, England, John Wright & Sons, 1932, p 105

5 Stewart, H L. Etiologic Studies in Hodgkin's Disease, *J Lab & Clin Med* **18** 281 (Dec) 1932

6 Wallhauser, A. Hodgkin's Disease, *Arch Path* **16** 522 (Oct), 672 (Nov) 1933

7 Steiner, P E. Hodgkin's Disease. Search for an Infective Agent and Attempts at Experimental Reproduction, *Arch Path* **17** 749 (June) 1934

8 Reed, D. On the Pathological Changes in Hodgkin's Disease, with Special Reference to Its Relation to Tuberculosis, *Johns Hopkins Hosp Rep* **10** 133, 1902

observed that the tuberculin tests performed on five of her eight patients with Hodgkin's disease were negative Simmons,⁹ Steiger,¹⁰ Corbeille,¹¹ Freer,¹² Bastai¹³ and others observed that most of their patients gave negative reactions to tuberculin cutaneous tests This has been used as evidence that Hodgkin's disease is etiologically unrelated to the tubercle bacillus

The reports of L'Esperance suggested the possibility that a comparison of the cutaneous reactions to human and avian tuberculins might give valuable information as to the etiologic rôle of the avian tubercle bacillus in Hodgkin's disease L'Esperance reported the results of such tests performed on twelve patients with various lymphadenopathies Seven of these gave positive reactions with avian tuberculin Only four of the seven had lesions histologically characteristic of Hodgkin's disease, so she was not impressed with the specificity of the reaction

Parker and his co-workers¹⁴ also compared the cutaneous reactions to human and avian tuberculins in a large series of cases of different lymphadenopathies They reported fewer positive reactions in patients with diseases of the lymphoid and myeloid tissues and with malignant disease than in normal persons and tuberculous patients They also found more positive reactions to the avian tuberculin than to the human except in the normal group

As part of a more extensive investigation begun during 1931 on the etiology of Hodgkin's disease, a comparison of the cutaneous reactions to old tuberculin derived from human and avian strains was made on these patients Later the highly purified tuberculin proteins (avian and human) prepared by Seibert¹⁵ were made available by her for these tests, and were used throughout the remainder of the investigation With these preparations quantitative tests of sensitization can be performed

9 Simmons, C C , Hodgkin's Disease, A Pathological Analysis of Nine Cases, *J M Research* **9** 378, 1903

10 Steiger, O Klinik und Pathologie der Lymphogranulomatosis (Paltauf-Sternberg) Beobachtungen und experimentelle Studien bei 9 Fällen von malignem Granulom, *Ztschr f klin Med* **79** 452, 1915

11 Corbeille, C Hodgkin's Disease in Children, *Minnesota Med* **11** 678 (Oct) 1928

12 Freer, W Lymphogranulom bei Kindern, *Jahrb f Kinderh* **123** 145 (March) 1929

13 Bastai, P Ueber die klinische Bedeutung der Tuberkulin Anergie bei malignem Lymphogranulom, *Klin Wchnschr* **7** 1606 (Aug 19) 1928

14 Parker, F , Jackson, H , Fitz-Hugh, G , and Spies, T Studies of Diseases of the Lymphoid and Myeloid Tissues IV Skin Reactions to Human and Avian Tuberculin, *J Immunol* **22** 277 (April) 1932

15 Seibert, F B , and Munday, B The Chemical Composition of the Active Principle of Tuberculin XV A Precipitated Purified Tuberculin Protein Suitable for the Preparation of a Standard Tuberculin, *Am Rev Tuberc* **25** 724 (June) 1932

The factor of variability of the potency and antigenicity of the test material according to the strain of organism or method of preparation used is eliminated. In this article the results of cutaneous tests performed on most of the patients in the cases reported in a previous communication, as well as on many others, are given.

EXPERIMENTAL WORK

Cutaneous tests with tuberculin protein (Seibert) performed on thirty-five patients with Hodgkin's disease, eleven with leukemia, three with lymphosarcoma, six with carcinoma, nine with tuberculous adenitis and nine with nonspecific adenitis form the basis of this report. In each case—except in some with leukemia—the diagnosis was made by histologic examination of diseased tissue of a lymph node by one or more disinterested, experienced pathologists.

The tuberculin proteins were given intracutaneously in test doses of 0.1 cc and the result observed in forty-eight hours. The first doses were 0.0001 mg of the proteins. If there were no reactions to these doses second injections were given, consisting of 0.001 mg. If at the end of another forty-eight hours this produced no reaction, third tests using 0.01 mg were made. By these tests it was planned to titrate the upper limit of sensitivity of the patients as indicated by the smallest amount of the tuberculin protein to which they would give a positive cutaneous reaction. After it became apparent that patients with Hodgkin's disease were never very sensitive to the protein, the smallest doses were omitted. There was no cause for regretting this because of any excessive reactions in subsequent patients.

This same antigen has been used in over two thousand persons—children and adults—in comparative tests with old tuberculin by Dr. Grace Hiller. She observed¹⁶ that the human tuberculin protein used in test doses similar to those reported in this article gave results similar to those obtained by the use of old tuberculin in comparative amounts. Occasionally the response to the tuberculin protein was greater than to old tuberculin, but the reverse also occurred.

The smallest amount used in these tests, 0.0001 mg of the tuberculin protein, is approximately equivalent to 0.1 cc of a 1:10,000 dilution of old tuberculin. Similarly 0.001 mg of tuberculin protein is approximately equivalent to a 1:1,000 dilution of old tuberculin and 0.01 mg of tuberculin protein to a 1:100 dilution of old tuberculin.

The results are given in the accompanying table. No case was observed in any group in which a positive reaction to the avian and a negative reaction to the human tuberculin protein occurred. In practically every group cases were seen in which there were reactions to the

¹⁶ Hiller, Grace. Personal communication to the author.

human protein and no reaction whatever to the avian protein. Greater reactions to the avian tuberculin protein than to the human protein occurred in a few cases in several groups, but this was a less frequent finding than the reverse (i. e., a greater reaction with the human than with the avian protein).

A wholly unexpected observation was made. Early in the study the comparative absence of cutaneous reactions in the group with Hodgkin's disease as contrasted with the control cases was observed. It is true that the control groups were much smaller and that accurate deductions are impossible. But this trend was definite, and persisted throughout the experiments. In no instance was a positive cutaneous reaction to 0.0001 mg. of the proteins observed in a patient with Hodgkin's disease. Few tests were performed with this, the smallest dose, because with the

Cutaneous Reactions to Tuberculin Protein

Diagnosis	Total No. Patients	0.0001 Mg. (1:10,000)					0.001 Mg. (1:1,000)					0.01 Mg. (1:100)				
		Patients Tested	Both Negative	Av = Hu*	Av > Hu	Av < Hu	Patients Tested	Both Negative	Av = Hu	Av > Hu	Av < Hu	Patients Tested	Both Negative	Av = Hu	Av < Hu	Av > Hu
Hodgkin's disease	37	2	2				33	23	1	2	3	23	20	2	1	3
Leukemia	11	3	0	2		1	9	5	1	1	2	6	2	1		3
Lymphosarcoma	3	1	1				3	2	1			2	0			2
Carcinoma	6	0					6	2			4	1	0			1
Tuberculous adenitis	9	5	1	1		3	8	0			6	1	0			1
Nonspecific adenitis	9	2	0	2			8	3			5	2	0	1	1	
Total	73															

* Av means avian and Hu, human tuberculin.

next larger dose of 0.001 mg. only six patients of thirty-three gave a reaction. In each of these six the reactions were very slight, so that a smaller test dose was not required to titrate the extent of the sensitivity. This is a large test dose for adults. However, when an even larger dose was used, namely, 0.01 mg. of the protein, twenty of twenty-eight patients tested failed to show sensitization. For adults this is an extremely large dose, and the failure of so many of the patients with Hodgkin's disease to react positively shows their extreme lack of sensitization. In the groups of cases other than Hodgkin's disease only a few patients were given this test dose because most of them had shown a reaction with smaller doses.

The statistical data fail to reveal several important observations. Although the reactions to the avian protein are occasionally charted as greater than those to the human protein, this difference was never very marked. On the other hand, there was occasionally a reaction to the human tuberculin-protein with an absence of reaction to the avian preparation.

The chart also fails to indicate the size of the reaction. In the patients with Hodgkin's disease who were sensitive to the test dose, the reaction was never large, and if the next larger test dose was given the response was not much greater. This behavior is unlike that of the sensitizations in most of the other groups. A patient with tuberculous adenitis who was barely sensitive to a certain test dose, if given the next larger dose, usually responded with a much greater reaction, even a maximal one with central necrosis.

In one case a "delayed reaction" was seen in a patient with Hodgkin's disease. There was no reaction to the first tests with 0.001 mg. when observed at forty-eight hours, so the largest dose of 0.01 mg. was then given. To this there was only a slight erythematous reaction in forty-eight hours. Three days later, however, a marked reaction was present at the sites of both tests. No similar reaction occurred in the other groups.

Repeated tests at intervals up to eight months were performed on some patients. Tests were also performed on a few patients before and after a series of roentgen treatments. No instance was noted in which a positive reaction occurred in a patient who had previously been insensitive. Neither did I see a reaction previously positive become negative.

COMMENT

It is generally recognized that if a large series of adults are given tuberculin tests with graded test doses, the largest of which is comparable in size to those used in the tests described, most of them give a positive reaction. This indicates sensitization to the tubercle bacillus or its products. The failure of patients with Hodgkin's disease to show this "normal" positive reaction can theoretically be explained in either of two ways. One possibility is that patients who acquire Hodgkin's disease are desensitized by the disease. If this is the correct explanation, this is the only chronic nontuberculous disease recognized at present that so regularly desensitizes its victims early while they are still in excellent general condition (certain tuberculous diseases of the skin are accompanied by an absence of cutaneous reaction to tuberculin¹⁷). The other possibility is that Hodgkin's disease occurs mainly in that small group of people in whom the "normal" adult sensitivity to tuberculin fails to develop. To prove this hypothesis it would be necessary to follow a large group of children to adult life with frequent tuberculin tests and observe whether Hodgkin's disease appeared only among those in whom a positive reaction never developed. In one patient in this series

17 Sulzberger, M. B. Sarcoid of Boeck (Benign Miliary Lupoid) and Tuberculin Anergy, *Am. Rev. Tuberc.* **28**: 734, 1933.

lesions of tuberculosis and of Hodgkin's disease were found in the same section of an excised lymph node. The patient was insensitive to tuberculin protein.

Regardless of which explanation is the correct one, it is difficult to conceive of this phenomenon occurring so regularly in a disease absolutely unrelated to tuberculosis. It cannot be attributed to the general condition of the patients because on the whole this was comparable in all groups. This failure of reaction was so marked that it was of value as presumptive evidence in diagnosis. It was of definite value in excluding tuberculous adenitis. It is offered as a valuable diagnostic procedure in the small group of patients who refuse biopsy and in whom it is advisable to exclude the possibility of active tuberculous adenitis before beginning treatment with large doses of roentgen rays.

The presence of a cutaneous reaction to the avian protein, found occasionally in each of the groups, must be explained. The experiments of Dolgopol¹⁸ help explain this situation. She found that the presence of a positive reaction to avian tuberculin observed in many cases of pulmonary tuberculosis did not indicate an active or latent mixed infection of human and avian tubercle bacilli. She considered the positive reactions to avian tuberculin as a group reaction caused by sensitization with the mammalian types of tubercle bacilli. She stated that an infection by avian tubercle bacilli might be assumed to exist when the reaction to avian tuberculin was positive while the reaction to other tuberculins was negative or considerably weaker. The last two conditions were not seen during the experiments reported in this paper.

The results obtained with the tuberculin protein differ from those reported by Parker and his co-workers, which they obtained with old tuberculin. The results agree in that fewer positive reactions were found in patients with diseases of the lymphoid and myeloid tissues, including Hodgkin's disease, and with carcinoma than in tuberculous patients. They differ from Parker's results in that in this series (1) fewer positive reactions were found in Hodgkin's disease than in the other lymphomas and carcinomas as well as in tuberculosis, and (2) there were fewer positive reactions to avian tuberculin protein than to the human protein. This discrepancy is probably due to the difference in antigenic capacity of the test solutions used.

SUMMARY

Tuberculin protein (Seibert) was used in performing intracutaneous skin tests on thirty-five patients with Hodgkin's disease (lymphogranulomatosis) and on thirty-eight controls with a variety of lymphoma

¹⁸ Dolgopol, V. B. The Specificity of Avian Tuberculin Reactions, *J. Infect. Dis.* **49** 216 (Sept.) 1931.

Tuberculin proteins prepared from both avian and human strains were used in comparative tests for the purpose of obtaining information on the possible etiologic rôle of the avian tubercle bacillus in Hodgkin's disease

No evidence of specific sensitization to the avian tuberculin protein was obtained in these tests. A marked desensitization (or absence of sensitization) was found to both proteins in the cases of Hodgkin's disease. This relative absence of "normal adult sensitization" was of diagnostic value, especially in the differential diagnosis of tuberculous adenitis. The incidence of absence of sensitization was greater in the group with Hodgkin's disease than in the groups of other lymphomas, which admittedly were small.

The interpretation was made either that (1) the process of Hodgkin's disease desensitizes its victims to these tuberculin proteins or that (2) Hodgkin's disease usually occurs in persons in whom development of the normal sensitization to the tuberculin protein is impossible.

It is difficult to conceive of either of these phenomena as occurring in a disease absolutely unrelated to tuberculosis.

CHRONIC SUPRARENAL INSUFFICIENCY

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In a recent article, we¹ reported a case of malnutritional edema which exhibited a unique clinical syndrome and a degenerative lesion of the suprarenal glands at autopsy. The outstanding clinical features of the syndrome were extreme emaciation with complete loss of body fat, asthenia, anorexia, polyneuritis, trophic ulcers, a high level of non-protein nitrogen in the blood, absence of pigmentation and hypotension. It was suggested that the syndrome was that of chronic suprarenal insufficiency, analogous to the similar state in animals produced by bilateral suprenalectomy.

That chronic suprarenal insufficiency is not a rare condition is shown by the fact that we are now able to report three additional cases, two of which have come to autopsy. Interest has also been aroused in another aspect of the syndrome. One of us (M P) has called attention to the resemblance in the later stages between pellagra and chronic suprarenal insufficiency.² Recently Thannhauser³ reported three cases of pellagra, in one of which an autopsy was performed by Aschoff.⁴ Aside from the disappearance of the body fat and atrophy of the internal organs, the only significant lesion found was marked atrophy of the suprarenal cortex.

REPORT OF CASES

CASE 1—G S, an Italian, aged 53, was admitted to the Gouverneur Hospital on Dec 11, 1932. The history, obtained through relatives, was that two months before admission he had eaten a condemned chicken and had since become progressively weaker. He had complained of anorexia and pains in the right thigh and in the costolumbar region.

Physical examination revealed a markedly cachectic, irrational, middle-aged man. Both lower extremities and the sacrum were moderately edematous. There

1 Packard, M, and Wechsler, H F. Chronic Adrenal Insufficiency, *Am J M Sc* **186** 66, 1933.

2 Packard, M. Discussion at Symposium on the Suprarenal Glands before the Section of Medicine, New York Academy of Medicine, Jan 17, 1933.

3 Thannhauser, S J. Pellagra und Endocrine Storungen, *Munchen med Wchnschr* **80** 291, 1933.

4 Aschoff, L. Pathologische-anatomische Bemerkungen zu dem vorausgehenden Aufsatz, *Munchen med Wchnschr* **80** 296, 1933.

was no pigmentation of the skin or visible mucous membranes. A prolonged Sergent white line was elicited. The pupils were dilated but reacted to light. There was bilateral ptosis of the eyelids. The fundi were normal. The breath was foul, the tongue was slightly coated and tremulous, and the teeth were carious.

The lungs were normal. The apex beat of the heart was in the fourth inter-space, 7 cm from the midsternal line. The sounds were of poor quality, but no murmurs were audible. The pulses were equal, regular and soft, and the pulse rate was 80. The blood pressure was 110 systolic and 70 diastolic. The abdomen was normal.

Quadripareisis, more marked in the lower extremities, was demonstrable. All the deep reflexes were absent with the exception of the finger jerks and the left knee jerk. The left abdominal reflex could not be elicited. The plantar reflexes were normal.

Laboratory Examination—The blood count revealed red cells, 4,750,000, hemoglobin, 66 per cent (Sahl), white blood cells, 5,000, neutrophils, 66 per cent, lymphocytes, 30 per cent, and mononuclears, 4 per cent. The urine had a specific gravity of 1.020, gave an acid reaction and showed no sugar but a trace of albumin, a few leukocytes and an occasional red blood cell. After sodium thio-sulphate was administered intravenously the urine contained 0.005 mg of arsenic and traces of lead. The Wassermann reaction of the blood was negative. The cerebrospinal fluid was clear and under normal pressure. It contained no globulin or sugar, and there were 16 cells per cubic millimeter. The Wassermann reaction and the colloidal gold tests were negative. Chemical examination of the blood plasma showed nonprotein nitrogen, 38 mg, and sugar, 100 mg.

Course—The course was progressively and rapidly downward. The loss of subcutaneous fat became more pronounced, but the skin retained its elasticity. A large bed sore quickly developed on the right buttock. The patient remained irrational and became very tremulous, involuntary athetoid movements in the upper extremities appeared. Five days after admission, signs of bronchopneumonia were evident, and the temperature rose steadily, reaching 106.6 F at the time of death on the seventh day.

Autopsy—The anatomic findings were cachexia with extreme loss of adipose tissue and atrophy of the internal organs, decubitus ulcer on the right buttock, chronic adhesive pleuritis, bronchopneumonia, dilatation of the right side of the heart, chronic perihepatitis and perisplenitis, congestion of the liver, chronic splenitis, petechial hemorrhages of the mesentery, idiopathic atrophy of the right suprarenal gland, and hypertrophy and degeneration of the left suprarenal gland.

The only vestige of the right suprarenal gland was a small piece of dark brown tissue, 8 mm in length. Histologic study of the sections revealed a thick capsule of fibrous tissue enclosing an extremely narrowed and distorted cortex. The cortex consisted for the most part of islands of greatly altered cortical cells separated by thick bands of hyaline fibrous tissue. Occasionally isolated cortical cells were found. Most of the cells were large with poorly staining, vacuolated cytoplasm and deeply staining, irregular nuclei. Other cells were deeply pigmented, and exhibited varying stages of necrosis. Between the cortical islands, and occasionally between the individual cells, were numerous lymphocytes and an occasional plasma cell. The medulla, although greatly reduced in size, was apparently normal.

The left suprarenal gland was enlarged, weighing 12.8 Gm, and on section had a grayish, homogeneous appearance. Microscopically the cortex was the seat of moderately advanced vacuolar degeneration, most marked in the inner layer of

the zona fasciculata and in the zona reticulata. The cortical cells in these areas were hyperplastic, and the cytoplasm was vacuolated. Necrosis was slight. The stroma was edematous and congested, contained a few small hemorrhages, and was scantily infiltrated with round cells. In the zona reticulata capillary and small venous thromboses were present. The medulla showed no changes.

Comment—The diagnosis of malnutritional edema is complicated in this case by the possibility of some form of poisoning. However, the absence of gastro-intestinal and renal symptoms, the negative observations with regard to these organs at autopsy and the quantitative analysis of the urine for heavy metals make this seem unlikely. The clinical syndrome is practically the exact counterpart of the case of chronic suprarenal insufficiency previously reported. The shorter course of the illness explains the fact that although the body fat was tremendously reduced, it had not entirely disappeared. The suprarenal lesion not only is of interest but probably accounts for the shorter duration of the disease. The pathologic changes in the right suprarenal gland are typical of those described in idiopathic suprarenal atrophy, the condition was obviously an old process. The cause of idiopathic suprarenal atrophy is unknown, when bilateral, it is usually accompanied by the symptoms of Addison's disease. The degenerative changes in the left suprarenal gland are similar to but less marked than those in our first case of malnutritional edema. As there was but one adequately functioning suprarenal gland, a moderate degeneration of this gland produced the syndrome of chronic suprarenal insufficiency.

CASE 2—F. S., an Austrian, aged 68, was admitted to the hospital on May 26, 1933, complaining of dyspnea, anorexia and pain in the right side of the chest. In 1925, after repair of a bilateral inguinal hernia, a cough developed. Roentgenograms of the chest, taken at that time, showed an enlarged heart and healed tuberculous lesions at both apexes. Since the operation the patient had suffered from constricting pains in the chest on exertion. For the past year he had had severe pains and stiffness in the joints of both hands, which had been treated with injections and by extraction of the teeth. For the past six weeks he had complained of increasing dyspnea on exertion and of occasional shooting pains in the right side of the chest. These pains were now continuous, and radiated down to the costal margin and around to the back. The loss of appetite was marked, and constipation was present. A frequent cough, productive of thick, whitish sputum, had developed recently. Nocturia was present.

Physical examination revealed a markedly undernourished, dyspneic, cyanotic, elderly man. In spite of emaciation the skin retained its elasticity. There was no pigmentation, and Sergent's white line was prolonged.

The pupils were equal and reacted to light and in accommodation. The eye-grounds showed moderate angiosclerosis. The tongue was coated, and the pharynx was slightly reddened. All the teeth were absent except two lower canines supporting a plate.

There was dulness to flatness over the entire lower right side of the chest, with absence of fremitus and breath sounds over this area. Slightly increased breath sounds and occasional moist rales were present above the area of dulness. The left side of the chest was hyperresonant.

The borders of the heart could not be determined accurately. The first sound at the apex was distant, of poor quality and totally irregular. A soft systolic murmur was audible over the aortic area which became intensified over the upper end of the sternum and in the neck. The pulses were equal and totally irregular, with a rate of 72, and the radial walls were thickened. There was no pulse deficit. The blood pressure was 140 systolic and 55 diastolic.

The abdomen was soft and showed the old hernial incisions. The liver was palpable two fingerbreadths below the costal arch. The lower pole of the right kidney was palpable. The right scrotal sac was filled with fluid. There were a few external tags about the anus. The prostate gland was not enlarged, and no masses were felt.

Marked clubbing of the fingers and atrophic arthritic changes in the metacarpophalangeal and the proximal interphalangeal joints were present. There was no edema.

Laboratory Examination—The blood count showed red cells, 4,740,000, hemoglobin, 80 per cent, white cells, 12,800, neutrophils, 84 per cent, lymphocytes, 14 per cent, and eosinophils, 2 per cent. Examination of the urine revealed albumin, 2 plus, and occasional hyaline and granular casts. The Wassermann reaction of the blood was negative. Chemical examination of the blood plasma showed urea nitrogen, 15.6 mg, and sugar, 74 mg. Tests of the sputum were repeatedly negative for tubercle bacilli.

An electrocardiogram showed auricular fibrillation and diffuse myocardial degeneration.

Roentgenograms of the chest revealed a thickened pleura and an effusion at the base on the right side and an enlarged heart. After the removal of the fluid and artificial pneumothorax the lower lobe of the right lung was collapsed, at the tip was a nodular elevation which suggested a malignant process. Proctoscopy and a barium sulphate clysma gave negative results.

The fluid removed from the effusion was straw-colored, and contained 1,810 white blood cells per cubic millimeter, with 20 per cent neutrophils and 80 per cent lymphocytes. The fluid was sterile on culture, and revealed no tumor cells.

Course—The patient suffered from extreme anorexia and asthenia, which were not improved by the administration of insulin and dextrose. The emaciation was progressive, and the loss of body fat was complete. A large bed sore developed over the sacrum. He complained of pains in the arms and legs, and the muscles and nerves of the extremities were extremely tender. The superficial and deep reflexes progressively diminished and finally disappeared. He became increasingly apathetic and tremulous. The blood pressure was stationary, and the signs in the chest were unaltered except for an increase in the effusion. On July 12, the urea nitrogen was 32 mg. The course was afebrile with the exception of two days in June, when, owing to impacted feces, there was a moderate fever. On July 5, the temperature rose to 102 F, and the fever continued irregularly to July 23, when the patient died. The temperature on the day of death was 99 F. He was irrational during the last week of the illness.

Autopsy—The anatomic diagnosis was decubitus ulcer of the sacrum, chronic adhesive pleuritis, hydrothorax on the right side, scirrhous adenocarcinoma of the right hyparterial bronchus with stenosis of the lumen, suppurative bronchopneumonia and chronic interstitial pneumonitis of the lower lobe of the right lung, emphysema of the left lung, healed apical tuberculosis, dilatation of the right side of the heart, advanced atherosclerosis of the aorta and coronary arteries, organ-

ized thromboses of the descending branch of the left coronary and of the right circumflex arteries, chronic myocardosis, a healed infarction of the lower two thirds of the left ventricle and the interventricular septum, with an early aneurysmal formation, chronic passive congestion and parenchymatous and fatty degeneration of the liver, chronic perisplenitis, acute and chronic splenitis, arteriosclerotic nephritis, prostatic hypertrophy, and carcinomatous metastases to both suprarenal glands, the paravertebral lymph nodes and the right kidney

The right suprarenal gland was enlarged to about the size of a woman's fist. On section it was entirely replaced by grayish-pink, homogeneous tumor tissue except for a thin rim in one area in which suprarenal tissue was still recognizable. The left suprarenal gland was somewhat larger and firmer than normal, and on section a nodule of tumor tissue was found at one pole. Microscopic examination of the right suprarenal gland showed the tumor to be an adenocarcinoma of the same structure as the carcinoma of the bronchus. Only a narrow rim of degenerating and necrotic suprarenal tissue remained. The left suprarenal gland exhibited, besides the tumor metastasis, marked vacuolar degeneration of the cortical cells and numerous small hemorrhages in the zona fasciculata.

Comment—The case exhibits all the classic features of chronic suprarenal insufficiency. There was no pigmentation, and the blood pressure was stationary throughout the illness, in spite of an old coronary occlusion and advanced myocardosis. The bronchial carcinoma was productive of many of the symptoms and in all probability played a rôle in the cachexia, but it could not conceivably produce the syndrome which is so exactly the counterpart of that occasioned by malnutrition. Miller and Jones,⁵ in a review of eight hundred and eight cases of carcinoma of the lung, found metastases to the suprarenal glands in 97 per cent of the cases. The complete replacement of one suprarenal gland and the partial involvement of the other by metastases furnish an adequate pathologic basis for the clinical picture.

CASE 3—B, a Jewish woman, aged 39, came under observation on Aug. 23, 1933. Her chief complaints were weakness and loss of weight. Nine years before, she began to suffer from "gas pains" and periodic attacks of nausea and vomiting. The vomitus would consist at first of food eaten and then of bile. Blood was never present. Roentgenograms of the gastro-intestinal tract were negative, and a diagnosis of gastric neurosis was made by several clinicians. The patient was placed on a restricted diet, especially in regard to vegetables, which the patient further reduced of her own accord. During the past year, she had had marked anorexia and four or five loose bowel movements daily without evident steatorrhea, and had lost 52 pounds (23.6 Kg.). Her weight at the commencement of the illness was 150 pounds (68 Kg.). She complained of extreme exhaustion and pain, stiffness, weakness and loss of power in all the extremities. Her former jovial disposition had changed to one of anxiety and apprehension, and she felt constantly depressed. Sexual desire was completely absent, and amenorrhea had been present for the past three months. A son had been asthmatic since birth, and was allergic to a number of foods.

5 Miller, J. A., and Jones, O. R. Primary Carcinoma of the Lung, *Am. Rev. Tuberc.* **21** 1, 1930.

Physical examination revealed a short, thin woman, who looked chronically ill. There was a complete loss of subcutaneous fat. The height was 59 inches (150 cm) and the weight 72 pounds (32.7 Kg). Freckles were present on the face, arms, abdomen and legs. There was no pigmentation of the visible mucous membranes. Serpentine's white line was present. The pupils were equal and regular and reacted to light and in accommodation. The thyroid gland was not palpable. The lungs were clear, and the heart was normal. The pulse was regular and soft with a rate of 68. The blood pressure was 78 systolic and 60 diastolic. There were no pathologic findings in the abdomen, but costovertebral tenderness was elicited. The knee jerks were sluggish, but there were no abnormal reflexes. Several anesthetic areas could be mapped out on the legs.

Laboratory Examination—The blood count revealed red cells, 4,400,000, hemoglobin, 85 per cent, and white cells, 9,000, normal differential count. The urine was essentially normal. Chemical examination of the blood plasma showed urea nitrogen, 32 mg, sugar, 112 mg, and creatinine, 1 mg. The Wassermann reaction of the blood was negative. The basal metabolic rate was minus 5 per cent. According to a test meal Ewald's technic showed moderate subacidity. Roentgenograms of the chest showed no signs of tuberculosis.

The patient is receiving treatment, which includes injections of a proprietary preparation of the cortical hormone three times a week and a diet high in vitamin B. In the short time she has been under observation, the patient has made considerable progress. She has gained 8 pounds (3.6 Kg), and the blood pressure is now 100 systolic and 75 diastolic.

Comment—This case could be classified as atypical Addison's disease. However, the complete loss of subcutaneous fat, the polyneuritis, the absence of pigmentation and tuberculosis and the history of malnutrition have led us to include it under the syndrome of chronic suprarenal insufficiency. The hypotension is difficult to explain except that this was our only case in a woman and, in all probability, in a hypotensive person. The encouraging response to treatment with extracts of the suprarenal cortex is of interest.

GENERAL COMMENT

Etiology—Three of the patients were men and one a woman. The respective ages were 50, 53, 68 and 39 years. Malnutrition was the apparent etiologic factor in three. As the hypertrophy and degeneration of the suprarenal glands in inanition and the various vitamin deficiencies have been commented on elsewhere, they need not be reviewed here. In one case the suprarenal glands were involved by a metastatic carcinoma. Addison⁶ recognized three causes of the disease which bears his name: tuberculosis, atrophy and carcinoma. Four of his eleven patients with the disease had malignant growths of the suprarenal glands. The clinical reports, however, are incomplete or lacking, and

6 Addison, T. A Collection of the Published Writings of the late Thomas Addison, London, The New Sydenham Society, 1868.

Wilks⁷ rejected these cases as true examples of the disease. Since that time the question as to whether carcinoma can cause the disease has been in dispute. The evidence against this assumption has been steadily accumulating with the advance in clinical and pathologic knowledge. In the older compilations of reported cases, such as Lewin's,⁸ a few are listed in this classification. The clinical and pathologic descriptions of these cases, however, are not convincing. Some cannot be considered as true Addison's disease, according to modern criteria, while in others the actual presence of a malignant tumor is doubtful. In all the recent large collections of reports of Addison's disease, verified by necropsy, such as those of Conybeare and Millis⁹ and Rowntree and Snell,¹⁰ carcinoma has not been found in a single instance. Addison⁶ was aware of the fact that malignant disease might exist in and partially or completely destroy both capsules without the appearance of pigmentation. The literature contains reports of many such cases. Rowntree and Snell¹⁰ stated that in seventy cases in which one or both glands were carcinomatous the clinical picture was not typical of Addison's disease. It is interesting to conjecture how many of these would fit into the syndrome of chronic suprarrenal insufficiency. Additional evidence that a malignant process can produce such a clinical picture is furnished by the primary tumors of the suprarenal cortex. In contrast to the usual obesity, cases are occasionally encountered in which extreme emaciation and loss of practically all the fat are seen.¹¹ It would seem that this is due to destruction of the suprarenal tissue, as the other symptoms of suprarenal hyperactivity are not so pronounced or are absent altogether.

Pathology—There were two significant findings at autopsy: an extreme to complete loss of body fat, accompanied by atrophy of the internal organs and a suprarenal lesion. The loss of fat was striking, involving not only the panniculus adiposus but also the internal fat depots. In the cases associated with malnutrition the suprarenal lesion was one of hypertrophy and degeneration. The latter change was evidenced by vacuolar degeneration of the cortical cells, with areas of necrosis and regeneration, and hyperemia, edema, hemorrhages and

7 Wilks, S. On Disease of the Suprarenal Capsules, or Morbus Addisoni, *Guy's Hosp. Rep.* **1** 63, 1862.

8 Lewin, G. Ueber Morbus Addisoni, *Charite-Ann.* **17** 536, 1891.

9 Conybeare, J. J., and Millis, G. C. Observations on Twenty-nine Cases of Addison's Disease Treated in Guy's Hospital Between 1904 and 1923, *Guy's Hosp. Rep.* **74** 369, 1924.

10 Rowntree, L. G., and Snell, A. M. A Clinical Study of Addison's Disease, Philadelphia, W. B. Saunders Company, 1931.

11 Cecil, H. L. Hypertension, Obesity, Virilism and Pseudohermaphroditism as Caused by Suprarenal Tumors, *J. A. M. A.* **100** 463 (Feb. 18) 1933.

capillary and venous thromboses of the interstitial tissue. What may have served as a contributory factor in one of the cases was the practically complete destruction of the right suprarenal capsule by idiopathic suprarenal atrophy.

Clinical Considerations—The early symptoms of the disease are profound anorexia, marked weakness, apathy and progressive loss in weight. There is no pigmentation of the skin or visible mucous membranes. A prolonged Sergent white line can be elicited. The wasting is extreme, and can continue until there is a complete loss of the body fat, the skin, however, retains its elasticity. The aversion to food is continuous and is not limited to any particular type, it is not accompanied by nausea, retching or vomiting. The disposition alters completely, the patient becoming increasingly morose, lethargic and desirous of death. Pains, paresthesias and weakness in the extremities develop, and the signs of polyneuritis, such as tenderness of the nerve trunks, diminution or absence of reflexes, areas of anesthesia and paresis of the limbs, become manifest. Trophic ulcers also make their appearance in spite of every precaution. The patient becomes delirious, and tremulous and athetoid movements are noted. Death is due to bronchopneumonia. The course is afebrile except for the onset of the terminal illness, and the final temperature is usually subnormal. Hypotension was lacking in the three cases verified by necropsy. In the woman now under observation the systolic blood pressure was only 78. Just as typical Addison's disease, in patients with coexisting essential hypertension, may occasionally be associated with high blood pressure, the low blood pressure in this case can best be explained by the occurrence of the syndrome in a hypotensive person.

Laboratory Findings—The only significant finding is moderately increased nonprotein nitrogen in the blood. Moderate secondary anemia is present.

Differential Diagnosis—The only disease that must be seriously considered in the differential diagnosis is Addison's disease. In 1855 Addison epitomized its signs and symptoms as follows: "The leading and characteristic features of the morbid state to which I would direct attention are anemia, general languor and debility, remarkable flabbiness of the heart's action, irritability of the stomach and a peculiar change of colour of the skin, occurring in connection with a diseased condition of the suprarenal capsules." In the three quarters of a century that has elapsed since then, little of importance has been added to this description. Addison's inclusion of anemia as a major symptom of the disease has been shown to be partially incorrect. There is rather a deficient circulation and utilization of oxygen, and, in the crises, a marked diminution in the volume of the blood is noted. The latter is associated

with a rise in the nonprotein nitrogen values of the blood. Hypotension has been added as a cardinal sign, and the frequent loss of weight and the occurrence of subnormal temperature have been emphasized by many clinicians. As would be expected in a syndrome based on diseased suprarenal capsules, chronic suprarenal insufficiency closely resembles this malady. The absence of many of the cardinal features, especially pigmentation and hypotension, plus the appearance of additional factors such as the practically complete loss of body fat, polyneuritis and trophic ulcers sufficiently differentiate the two conditions. So-called atypical cases of Addison's disease are not uncommon, and it is for future observation to decide whether many of these do not rightly belong under the classification of chronic suprarenal insufficiency, particularly those based on malnutrition or carcinoma.

Pituitary cachexia offers little difficulty in the differential diagnosis, as the disease runs an exquisitely chronic course, and the emaciation is accompanied by wrinkling of the skin, falling out of the hair and teeth and atrophy of the genitalia. In multiple sclerosis of the endocrine glands, symptoms of both myxedema and suprarenal insufficiency are added to those of pituitary cachexia.

Treatment—In only one case has specific therapy been attempted. With the use of a proprietary preparation of the cortical hormone and a diet high in vitamin B, encouraging results are being obtained.

SUMMARY

Three additional cases of chronic suprarenal insufficiency are reported, and the entire group is analyzed. The etiology, pathology, symptoms, differential diagnosis and treatment are discussed.

CHRONIC ARTHRITIS

SEROLOGIC AND CLINICAL STUDIES

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The present investigation was initiated to establish a better understanding of the serology of chronic arthritis and, more particularly, the arthritis that has been considered infectious. Our interest centered on four major topics: (1) the specificity and sensitivity of the streptococcic agglutination reaction in chronic infectious arthritis, as reported by Cecil, Nicholls and Stainsby¹ and confirmed by Dawson, Olmstead and Boots,² (2) the relation between agglutinin titer and cutaneous sensitivity, (3) the relation between agglutinin titer and clinical course, and (4) the effect of vaccine treatment on agglutinin titer.

Organisms of four types commonly isolated by our laboratory from foci of infection in patients with chronic arthritis were selected for this study. In addition, we chose members of three bacterial groups which are frequently implicated, according to the reports of leading authorities on the disease.

SELECTION OF ORGANISMS

The following brief résumé of the literature serves to indicate the diversity of current opinion regarding the organisms involved in arthritis and the organisms recommended for vaccine therapy. During the last fifteen years, many clinicians and bacteriologists have attempted to isolate the causal factor in cases of arthritis, using as source material blood, fluid and tissues from the affected joints and secretions and excretions from other loci as numerous as the parts of the human body. The organisms isolated are of many different genera. Those most often reported are, in order of frequency: streptococci of the hemolytic, viridans and anhemolytic types, diplococci, diphtheroids, staphylococci, intestinal organisms of the colon-typhoid group, gonococci, pneumococci.

From the Desert Sanatorium and Institute of Research

1 Cecil, R. L., Nicholls, E. E., and Stainsby, W. J. *Bacteriology of Blood and Joints in Chronic Infectious Arthritis*, *Arch. Int. Med.* **43**: 571 (May) 1929, *J. Exper. Med.* **50**: 617, 1929, *Am. J. M. Sc.* **181**: 12, 1931.

2 (a) Dawson, M. H., Olmstead, M., and Boots, R. H. *Proc. Soc. Exper. Biol. & Med.* **28**: 419, 1931, (b) *ibid.* **28**: 421, 1931, (c) *J. Immunol.* **23**: 187, 1932, (d) *ibid.* **23**: 205, 1932.

and even anaerobes of the *Clostridium Welchii* group. An exhaustive summary of the bacteriologic observations in atrophic arthritis may be found in the *Annals of the Pickett-Thomson Research Laboratory*,³ and the critical reviews of the subject by Jordan and Vrtiak and Jordan⁴ and by Miller⁵ are complete. The reader is also referred to "A Symposium on Arthritis"⁶

Recently stress has been laid on the streptococci by the reports of Cecil and his associates¹ that they have isolated with considerable regularity from the blood and joints of patients with atrophic arthritis a strain of *Streptococcus haemolyticus* which is of a constant cultural character, agglutinates readily with the serums of patients with atrophic arthritis and produces a disease similar to atrophic arthritis when injected intravenously into rabbits, it has been chosen by Cecil as a therapeutic agent in the form of vaccine in selected cases. Dawson, Olmstead and Boots were unable to isolate a significant organism from cultures of the blood, joints or nodules in a series of 80 patients with arthritis.^{2a} They found, however, that Cecil's typical hemolytic streptococcus is agglutinated by serums from patients with atrophic arthritis in the great majority of cases to a high titer, and that other hemolytic streptococci of the scarlatinae-erysipelas group agglutinate equally well.⁷ They found no evidence of a specific reaction which could differentiate any of the hemolytic strains examined. Burbank and Hadjopoulos,⁸ following Hastings,⁹ are strong proponents of the complement-fixation reaction as an aid in the diagnosis and treatment of arthritis. They reported that serums from patients with atrophic arthritis bind complement with certain stock and autogenous hemolytic streptococci which they isolated from the blood, feces, urine or local lesions (in teeth, tonsils and other localities) of patients with atrophic arthritis. In addition, they stated that a patient is often improved by treatment with a vaccine made from the streptococci which show fixation with his serum. They recently published the results of experiments in which rabbits artificially infected with hemolytic or green-producing streptococci cul-

3 Thomson, D., and Thomson, R. The Pathogenic Streptococci, Ann Pickett-Thomson Research Lab., 1929, vol. 4, pts. 1 and 2

4 Jordan, E. P. Microbic Etiology of Rheumatic Fever and Arthritis, Arch Path **10** 79 (July) 1930. Vrtiak, E. G., and Jordan, E. P. Clinical Study of Chronic Arthritis, J. A. M. A. **94** 863 (March 22) 1930.

5 Miller, J. L. Am J M Sc **182** 158, 1931

6 Symposium on Arthritis, J. Lab & Clin Med **15** 1055 (Aug.), 177 (Sept.) 1930

7 Dawson, Olmstead and Boots (footnote 2 b, c and d)

8 Burbank, R., and Hadjopoulos, L. G. Serologic Significance of Streptococci in Arthritis and Allied Conditions, J. A. M. A. **84** 637 (Feb. 28) 1925, J. Lab & Clin Med **14** 131, 1928

9 Hastings, T. W. J. Exper Med **20** 52, 1914

tured from the blood of patients with arthritis manifested the typical symptoms and pathologic changes of arthritis, the injected organisms could regularly be recovered from the animals' joints and could be demonstrated within the synovial tissues and bone tissues of the affected parts¹⁰ Some of the arthrotropic streptococci isolated by Crowe¹¹ have been compared with the strains of Burbank and are said to be similar or identical¹² Attempts to culture significant bacteria from the blood of arthritic patients by the method of Cecil, Nicholls and Stainsby¹ have failed in our laboratory¹³

MATERIALS AND TECHNIC

History and Characteristics of Cultures—Originally 7 organisms were selected They included Cecil's typical arthrotropic hemolytic streptococcus strain AB 13,¹⁴ the NY 5 strain of *Str. scarlatinae*,¹⁵ Cecil's anhemolytic streptococcus RB 5¹⁴ and 4 organisms isolated from patients in the Desert Sanatorium, the hemolytic streptococcus W and *Bacterium coli* H were isolated repeatedly by us from the fresh stools of 2 patients in far advanced stages of atrophic arthritis, *Str. viridans* M was isolated from the throat and repeatedly in almost pure culture from the rectal mucosa of a young man with a long history and advanced symptoms of spondylitis *Staphylococcus aureus* P was for more than a year the characteristic organism in the nasal discharge in a severe case of chronic sinusitis (nonarthritic) In addition to the 7 organisms listed, several other streptococci which had been isolated from cases of atrophic arthritis in representative laboratories were employed during the preliminary work, but were discarded because of their failure to produce significant serologic or cutaneous reactions *Str. haemolyticus* NY 5 was abandoned early, since it gave evidence of a biochemical and serologic relationship to AB 13, always reacting with serums which agglutinated Cecil's organism, but always in lesser degree The cultural characteristics of the remaining streptococci are shown in table 1 They remained constant, with the exception of *Str. viridans* M, which of late has tended toward the hemolytic type *Bact. coli* H is of the communis variety and is an active hemolyzer, *Staph. aureus* P is typical in the production of pigment and occasionally hemolyzes blood agar

Agglutinating serums for each of these streptococci were prepared by repeatedly inoculating rabbits with killed and live young organisms Injections were made on four consecutive days each week for from six to twelve weeks, beginning with minimal doses and reaching a maximal approximate dose of from 5,000,000,000 to 10,000,000,000 organisms With this technic, no agglutinin titers above 1,280 were obtained Absorption of agglutinins in these serums by the 4 streptococci indicated that *Str. haemolyticus* AB 13 and *Str. haemolyticus* W were separate serologic entities Absorption of AB 13 serum by the heterologous organisms did not greatly diminish AB 13 agglutinins *Str. haemolyticus* W differed from the

10 Hadjopoulos, L. G., and Burbank, R. J. *Bone & Joint Surg.* **14** 471, 1932.

11 Crowe, Warren. *Ann. Pickett-Thomson Research Lab.* **4** 398, 1929.

12 Thompson, David. *J. Lab. & Clin. Med.* **11** 1117, 1931.

13 Mote, J. Unpublished communication to the authors.

14 These organisms were obtained through Dr. Stainsby, they were isolated in his laboratory from patients with atrophic arthritis and rheumatic fever, respectively.

15 This organism was isolated by Dr. Dochez from the throat of a patient with scarlet fever and obtained through Dr. Boots' laboratory.

other streptococci in that it was repeatedly pathogenic for rabbits, killing them regularly within three or four days with evidence of septicemia and renal involvement when doses of approximately from 1,000,000,000 to 5,000,000,000 organisms were given. No other streptococcus tested was lethal for rabbits in the doses given.

All of the organisms used in agglutination tests were from fresh live broth cultures. The streptococci were transferred at one or two day intervals to beef heart broth pH 7.6, prepared according to the technic of Nicholls and Stainsby,¹⁶ to which was added fresh citrated rabbit blood, 5 per cent by volume. Antigen flasks containing 80 cc of beef heart broth were inoculated from "starter" blood-broth cultures of streptococci which were in the initial period of logarithmic growth (from five to six hour cultures) and were incubated for twenty-four hours before use. We soon discovered that more vigorously growing, diffuse and stable

TABLE 1—*Cultural Characteristics of Streptococci Used in Agglutination and Skin Tests as a Routine*

Organisms	Morphology of Organisms	Morphology of Colony	Zone on Blood Agar	Sugar Fermentation		Milk
				Mannite	Inulin	
Str haemolyticus AB 13	Long chains, cocci round, varying markedly in size in same chain	Finely granular, small, undulant, intermediate SR	Narrow zone of incomplete hemolysis	—	—	A
Str haemolyticus W	Short chains, cocci large, often lance shaped	Large, mucoid, dewdrop, smooth	Wide zone of vigorous hemolysis	+	+	A
Str viridans M	Short chains, cocci round and lance shaped	Pinpoint, flat, round, smooth	Good production of methemoglobin	—	+	C++
Str anhaemolyticus RB 5	Long chains, cocci usually round, occasional bacillary forms		Indefinite production of methemoglobin	—	+	A C+

All of the streptococci produced acid without gas in dextrose, lactose, sucrose and salicin, all were bile insoluble and did not liquefy gelatin.

Acid formation and no gas are denoted by +, no acid formation and no gas, by —, acid formation and no clot, by A, acid formation and hard clot, by AC, and extensiveness of clotting by C+ or C++.

antigens could be obtained in the following manner. The broth was buffered with 5 per cent dibasic potassium phosphate, and 1 per cent dextrose was added at the time of inoculation, after the supernatant homogeneous suspension was incubated for not more than twenty hours it was decanted and the reaction readjusted with double normal sodium hydroxide to pH 7.6. Occasionally the streptococci agglutinated spontaneously even with these precautions, but this difficulty was generally overcome by rapid transfer twice a day in blood broth for from six to ten days. Satisfactory staphylococcus and *Bact. coli* agglutinogens were readily prepared in ordinary veal infusion broth, pH 7.4, which was incubated from eighteen to twenty-four hours.

Antigens for skin testing and vaccine therapy were made from organisms grown as for agglutination, concentrated by centrifugation, washed four times in 5 per cent phenol-saline and resuspended to a standard density in phenol-saline solution. After standardization by direct count and sterility tests, the antigens were released for clinical use.

Technic—Serums for agglutination tests were collected by one of us from arthritic and control groups and sent under serial number to the laboratory. After the first short series, scrupulous care was taken that the clinician and the serologist should not know each other's results until the tests were completed. Final concentrations of the serum after the addition of antigen ranged from 1/40 to 1/2,560, as a routine, the final volume per tube was 1 cc. Tests were incubated in a constant-level water bath at 56° C for two hours, then refrigerated overnight and read approximately eighteen hours after being set up. Readings immediately after incubation in a water bath were not sufficiently definite, owing to the slow formation of readily visible aggregates. All readings were made by one observer with the naked eye, then checked with a magnifying double-prism optician's loupe. The highest dilution in which definite, well formed clumps of micro-organisms could be seen was considered the serum titer.

RESULTS

In analyzing our data on patients with arthritis it seemed advisable to us to use the system of clinical grouping which was developed by Dr. Holbrook¹⁷ in the Desert Sanatorium and Institute of Research and which has proved to be practical and helpful to us in selecting therapeutic measures. We present the following brief summary of his classification, in which atrophic arthritis is divided into two groups. Group 1 is an afebrile, insidious, progressive, symmetrical deforming and crippling disease. Group 2 is a febrile disease, often acute in onset, with heat, redness and swelling of the joints. Group 3 is commonly designated as osteo-arthritis, hypertrophic arthritis or degenerative arthritis. Group 4 A is spondylitis without bony ankylosis. Group 4 B is spondylitis with bony ankylosis. Group 5 is often termed metabolic, traumatic or menopausal arthritis, ordinarily with involvement of only one joint. Group 6 may properly be termed prearthritis, and in it are included all of the manifestations of neuritis, myositis, bursitis, fibrositis and similar conditions.

Sixty-seven cases of arthritis (all forms) fell readily into definite clinical groups. From these a total of 259 specimens were collected and tested for agglutinins against the 6 selected type organisms. The control group comprised 119 patients, from whom 174 specimens were collected. It will be seen from tables 2 and 3 that Cecil's hemolytic streptococcus AB 13 reacted in high serum dilution with 70 per cent of the serum specimens of types I and II, and with the specimens from about 75 per cent of the cases in these groups. This is a markedly higher frequency than was demonstrable with any of the other antigens. In no other clinical group was the percentage of high AB 13 titers so remarkable, the only runners-up being group 4 A, which may be atrophic arthritis of the spine, and the group of rheumatic infections. Except in cases of atrophic arthritis the agglutinins against AB 13 are infre-

¹⁷ Holbrook, W. P. *Southwestern Med* 16:149, 1932.

TABLE 2—Percentages of Clinically Grouped Specimens Which Agglutinate with Selected Micro-Organisms

Clinical Diagnosis	Str Haemolyticus AB 13			Str Haemolyticus W			Str Viridans M			Str Anhaemolyticus RB 5			Staph Aureus P			Bact Coli H		
	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +	Total Specimens	+320 or Over	All +
Arthritis Groups																		
Type I	59	71	88	59	8	41	59	19	61	58	33	69	59	5	54	58	12	26
Type II	138	70	90	135	13	45	133	9	61	133	49	84	135	4	42	128	8	30
Type III	13	8	31	11	9	18	11	0	9	11	18	64	11	0	9	9	(1)	(1)
Type IV A	37	43	65	35	50	75	36	1	42	36	25	89	36	3	25	36	3	11
Type IV B	6	(0)	(1)	5	(1)	(2)	5	(0)	(0)	5	(0)	(2)	5	(0)	(0)	4	(0)	(0)
Type V	6	(0)	(2)	5	(0)	(2)	5	(0)	(0)	5	(2)	(5)	1	(0)	(1)	5	(0)	(0)
Control Groups																		
Normal	49	0	2	6	(2)	(5)	6	(0)	(1)	6	(2)	(4)	6	(0)	(1)	6	(0)	(0)
Tuberculosis	23	0	4	3	(1)	(1)	2	(0)	(0)	3	(1)	(2)	3	(0)	(0)	2	(0)	(0)
Other diseases*	34	6	12	13	15	62	13	8	31	12	25	81	13	0	0	11	0	27
Rheumatic infections, type VI, etc	26	15	23	21	10	48	21	0	14	19	10	63	21	0	14	17	0	0
Acute streptococcal diseases, sinusitis	42	5	12	7	(0)	(5)	7	(0)	(4)	7	(2)	(6)	7	(0)	(1)	7	(0)	(0)

The figures in parentheses represent actual numbers

* These diseases were asthma, obesity, cardiovascular renal disease and similar conditions

TABLE 3—Percentage of Clinically Grouped Cases Yielding Serums Which Agglutinated with Selected Micro-Organisms (Based on Highest Agglutinin Titers for Each Case)

Clinical Diagnosis	Str Haemolyticus AB 13			Str Haemolyticus W			Str Viridans M			Str Anhaemolyticus RB 5			Staph Aureus P			Bact Coli H		
	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +	Total Cases	+320 or Over	All +
Arthritis Groups																		
Type I	14	71	86	14	21	57	14	29	57	13	31	62	14	14	50	13	31	46
Type II	27	81	96	27	15	67	27	26	70	27	48	89	27	19	59	25	16	40
Type III	12	8	33	10	10	20	10	0	10	10	20	70	10	0	10	8	(1)	(1)
Type IV A	7	(2)	(4)	7	(2)	(4)	7	(1)	(2)	7	(2)	(6)	7	(1)	(3)	7	(1)	(3)
Type IV B	2	(0)	(1)	2	(1)	(1)	2	(0)	(0)	2	(0)	(1)	2	(0)	(0)	1	(0)	(0)
Type V	5	(0)	(2)	5	(0)	(2)	2	(0)	(0)	1	(2)	(1)	3	(0)	(1)	2	(0)	(0)
Control Groups																		
Normal	39	0	3	6	(2)	(5)	6	(0)	(1)	6	(2)	(4)	6	(0)	(1)	6	(0)	(0)
Tuberculosis	18	0	5	3	(1)	(1)	2	(0)	(0)	3	(1)	(2)	3	(0)	(0)	2	(0)	(0)
Other diseases (general)	26	4	8	7	(2)	(4)	7	(1)	(3)	7	(3)	(7)	7	(0)	(0)	5	(0)	(1)
Rheumatic infections, type VI, etc	16	25	31	11	18	64	11	0	18	10	20	70	11	0	27	7	(0)	(0)
Acute streptococcal diseases, sinusitis	20	10	25	7	(0)	(5)	7	(0)	(4)	7	(2)	(6)	7	(0)	(1)	7	(0)	(0)

The figures in parentheses represent actual numbers

quent, when they occur in other clinical conditions, the titer is generally low and disappears rapidly

In 28 cases of atrophic arthritis, in which the serums were tested against AB 13 at regular intervals average agglutinin titers for each patient were computed. Ninety per cent of the cases showed an average titer of 1:320 or more, and in 100 per cent the reactions were positive in some degree. Forty random cases from all other groups were followed in a similar manner, and only 38 per cent showed a reaction, in 10 per cent the reaction was positive in high degree. The percentages were of course increased by the inclusion of group 4 A and the cases of rheumatic infection. Exclusive of these, the control figures are: positive reactions of any degree, 26 per cent of 30 cases, high positive reactions, 3 per cent.

The peak and average titers in 33 of 41 cases of atrophic arthritis were in general significantly higher for AB 13 than for any other test organism. The 8 remaining cases gave lower reactions with AB 13 than with other test organisms. Of the 8, 3 were definitely arrested cases, in 1 the patient had recovered, in 1 a high selectivity for *Bact. coli* H was consistently maintained, and 3 were active typical cases.

Because of a possible influence on agglutinin titers, all of the histories were searched for records of previous or concomitant streptococcal infections and of previous administrations of streptococcus vaccine. In groups 1 and 2 we were unable to find any subjects with a history of recent proved streptococcal infection, sore throats and colds being noticeably absent. There were only 12 patients of groups 1 and 2 to whom assuredly no vaccine had been given previous to the time of agglutination. Of these, 10 patients (83 per cent) proved to have high titer agglutinins for AB 13. Repeated agglutinin titers were determined at intervals on 46 patients with arthritis, 28 of whom had atrophic arthritis. In this group there was no regular correlation between agglutinin titer and clinical course. The agglutinin titer was seen to rise, fall or remain constant regardless of whether the clinical condition became worse or better or remained the same.

Our data, on analysis, showed no greater frequency of positive agglutinin reactions in the older patients than in the younger.

CUTANEOUS REACTIONS

To determine the number of organisms to be injected for cutaneous reactivity a group of 15 normal subjects was tested with phenol-saline preparations of the 6 different organisms previously described. In the case of AB 13 it was found that all normal subjects gave a small positive reaction to a dose of 20,000,000 organisms per one-tenth cubic centimeter injected intracutaneously. When the dosage was reduced to

2,000,000 organisms, there were no positive reactions in the normal group. The skin test dose of 2,000,000 organisms was thus established and for uniformity was used with all autogenous and other stock organisms in testing patients. Readings were made at thirty minutes and at twenty-four and forty-eight hours. The induration and erythema of all of the reactions were measured and recorded in degrees from 1 plus to 4 plus. The standards for measurement were selected arbitrarily. Induration of from 0.4 to 0.7 cm. or erythema of from 0.6 to 1.5 cm. was considered 1 plus. Reactions with an induration of 1.9 cm. or erythema of 3.6 cm. or more were classed as 4 plus.

With the stock vaccines the positive reactions were few and scattered, without predominant reactions to any one organism in the arthritic group or in the controls. In the case of AB 13, 16 per cent of all patients with arthritis (i. e., 67) gave a positive reaction. In 31 cases of atrophic arthritis, 20 per cent of the patients gave positive reactions. This is higher than the percentage of positive reactions in the control group, but was not considered great enough to be of much significance. Surveying all of the cases, there was no apparent correlation between the skin test and the agglutinin titer.

In general, the group of patients with atrophic arthritis were strikingly anergic or nonreactive to the various organisms, both stock and autogenous. Only in rare instances was a cutaneous reaction to stock vaccine as strikingly positive as the reaction to the same number of autogenous organisms. In many instances the skin reacted to the autogenous organisms and not to the stock organisms when the dose was the same and the morphologic and cultural characteristics were similar. Positive reactions occurred more frequently with hemolytic gram-negative bacilli isolated from stools than with any other autogenous organisms.

TREATMENT WITH VACCINE

So much has been written about treatment with vaccine when all kinds of organisms, dosages and methods are used, that no attempt will be made to cover the literature. Except for a few well controlled experiments, the outstanding feature is the great diversity of reports. Many authors overlook the natural tendency in early cases to exacerbation and spontaneous remissions, which probably accounts for many of the reported cures and improvements. Sixty per cent of the 1,000 patients with arthritis who have been examined at the Desert Sanatorium recovered from the first attack¹⁸. The patients who were made worse by large doses of vaccine or nonspecific protein therapy were probably not reported. In our experience the best results have followed

18 Holbrook, W. P. Evaluation of Therapy in Chronic Atrophic Arthritis, *Ann Int Med* 7:457 (Oct) 1933.

desensitization of patients who have shown marked cutaneous sensitivity to an autogenous organism and occasionally to a stock organism. We have also observed that with subcutaneous and intramuscular injections the patient may do well for a time, but too often more sensitivity will develop. Clinically, there are increasing specific reactions to vaccine and increased cutaneous sensitivity to smaller doses.

On the basis of the aforementioned experiments and the experiments of Clawson and Weatherby¹⁹ on animals, it was decided to confine treatment in this series to desensitizing doses by the intravenous route. Though we are aware that phenol-saline vaccine may not be the

TABLE 4—*Serologic and Clinical Observations on a Few Representative Cases of Atrophic Arthritis*

Case	Duration, Years	Organisms Used in Treatment	Duration of Treat- ment, Months	Maximum Number of Organisms	Clinical Reac- tion to Vaccine	Skin Test		AB 13 Titer		Clinical Result
						Before Vac- cine	After Vac- cine	Before Vac- cine	After Vac- cine	
Stock										
191	3	AB 13	4.5	50,000,000	0	+	0	1,280	1,280	Improved
186	6	AB 13	3.5	20,000,000	0	0	0	0	2,560	Improved
210	20	AB 13	1.0	30,000	+	++++	0	640	320	Worse
215	10	RB 5	2.0	1,000,000	0	0	0	640	1,280	Improved
176	26	B coli H	4.0	100,000,000	+	++	0	640	1,280	Improved
181	4	B coli H	5.0	100,000,000	+	+	0	640	640	No change
205	10	B coli H	2.0	5,000,000	+	++	0	640	640	Improved
207	13	B coli H	1.0	100,000	0	0	0	320	320	No change
Autogenous										
202	2.5	Str haemo- lyticus W	4.0	5,000,000	0	++++	0	0	2,560	No change
213	8	Hemolytic gram nega- tive bacilli	1.5	160,000	+	++++	0	1,280	160	Improved
183	14	Hemolytic gram nega- tive bacilli	5.0	10,000,000	+	++++	0	640	160	Improved
180	3	Hemolytic gram nega- tive bacilli	4.0	20,000,000	+	++++	++	640	1,280	Improved

ideal or correct preparation, we have used it because of our experience with it.

Comparable groups treated and untreated with vaccine were chosen for observation. All of the cases were chronic and of several years' duration. In addition each group was further subdivided to contain groups of patients with and without positive cutaneous reactions and groups of patients with and without positive agglutinin titers. All of the cases in which other modes of therapy might complicate the picture were ruled out.

In table 4 are listed observations on some of the typical cases of groups 1 and 2. The vaccine was given intravenously twice weekly,

¹⁹ Clawson, B. J., and Weatherby, M. Experimental Basis for Intravenous Vaccine Therapy in Chronic Arthritis with Summary of Results Obtained in Patients, *Ann Int Med* 5:1447 (June) 1932.

starting with approximately 100 organisms and gradually increasing to the maximum approximate dose listed over the period mentioned. An attempt to avoid apparently specific clinical reactions was made, though some reactions were noted with intravenous injections as low as from 30,000 to 50,000 organisms. Prior to and during the course of vaccine therapy repeated skin tests and agglutinin determinations were made on all of the patients. Cutaneous reactions and agglutinin titers before and after therapy were tabulated. The duration of therapy as listed does not represent the time during which the patients were under observation, as explained, all of the cases were chronic, and it is of importance that all of them were without significant change clinically for a period of at least a few months before the treatment with vaccine was started. In our experience the patients who respond well to vaccine show evidence of it within a month or two.

RESULTS OF TREATMENT WITH VACCINE

So far in this work we have not a sufficiently large group of well controlled cases from which to draw conclusions of much clinical significance. Several observations were made, however, that are worth noting. Sensitivity to a particular organism was reduced in every case following the intravenous administration of the same organism, this desensitization did not occur in a few instances in which heterologous organisms were given intravenously or in which homologous organisms were given subcutaneously. There was no regularity in changes of agglutinin titer during or after treatment with vaccine, the titer increased, decreased or remained constant without apparent relation to the treatment with vaccine or the clinical course. The clinical course of the patient and the result listed in the table may or may not be due to treatment with vaccine, for here again comparable groups of patients not receiving vaccine did quite as well. Skepticism is invited because of the well known psychologic effects of a new treatment on patients with chronic conditions. There is no case in the table or in the balance of unlisted patients in which improvement could not have been caused by some factor or factors other than vaccine. We believe, however, although we cannot prove, that in some of the patients who showed marked cutaneous sensitivity, significant improvement followed desensitization. The improvement that seemed most probably due to treatment with vaccine was obtained with autogenous organisms only.

COMMENT

The foregoing observations on a representative group of arthritic patients indicate that *Str. haemolyticus* AB 13 has a closer serologic relation to atrophic arthritis than any other organism studied. This is in agreement with the reports of Cecil and his co-workers and the

experiments of Dawson and Boots. We feel that the relatively high percentage of positive reactions with RB 5 was insignificant, as it showed no selectivity for any clinical group. Other organisms were of possible serologic interest only in isolated cases.

If there is a definite bacterial agent responsible for arthritis, three possibilities occur to us in explanation of the serologic behavior of AB 13 in the disease. 1. It is the cause of atrophic arthritis, recognizing that highly selective serologic reactions are not necessarily indicative of etiologic relations, we feel that definite deductions on this point would be premature. 2. In specific protein content, AB 13 is related to this agent. 3. AB 13 may be a secondary invader, its existence made possible in the human body by the previous production of highly specific conditions favorable to its growth. Such conditions once established, antigen could readily be released into the system, producing apparently specific agglutinins. In this connection it must be remembered that this streptococcus is not a common inhabitant of the human body, and that it cannot readily be cultured from any of the common sources.

It seems probable that the occurrence of AB 13 agglutinins in atrophic arthritis is not solely explainable on the basis of so-called normal antibodies. The AB 13 titer is in a large percentage of cases of atrophic arthritis within a titer range generally considered indicative of serologic specificity (320 or more), while in other clinical groups tested the serum titers for this organism are uniformly low or negative. The AB 13 titers of serums from patients with atrophic arthritis are higher than titers for any other organisms employed in this study, although the remaining organisms, particularly *Staph aureus* and *Bact coli*, occur among the common flora of the human body. Mackie and Finkelstein²⁰ and Gibson,²¹ in their discussions of the natural phenomena of immunity, agreed that normal antibodies, though occurring frequently in the blood of various mammals, are most readily demonstrable for bacteria of the intestinal groups. We found few agglutinins against *Bact coli* and *Staph aureus* in the atrophic group. Gibson reported no natural agglutinin titers higher than 320 except in a few cases with *Bacillus pyocyaneus* and *Bacterium dysenteriae*, his series comprised a large and representative group of bacterial species. He further stated that the serums of young animals are deficient in natural agglutinins. We were unable to demonstrate that the age group plays a part in the occurrence of AB 13 agglutinins in the patients with atrophic arthritis or in the remainder of the clinical groups studied, this is contrary to a recent report by Dawson, Olmstead and Boots.

The absence of correlation between agglutinin titer and cutaneous sensitivity in arthritis is not surprising when one considers that such a

20 Mackie, T. J., and Finkelstein, M. H. *J. Hyg.* **30** 1, 1930.

21 Gibson, H. I. *J. Hyg.* **30** 337, 1930.

relation is not reported in other chronic diseases. We have frequently noted that cutaneous sensitivity diminished with the intravenous administration of vaccine, but that the agglutinin titer showed no corresponding variations.

There was no correlation between agglutinin titer and cutaneous reaction in a group of over 100 patients, all of whom were tested by the two methods simultaneously at least once. The same finding applies to a group of 31 atrophic patients tested in a similar fashion at weekly intervals for several months. Likewise, Keefer, Myers and Oppel,²² in using the nucleoprotein of *Str. scarlatinae*, found no correlation between skin tests and agglutinations.

It has been reported that a fall in the agglutinin titer often accompanies clinical improvement. We are not able to substantiate this observation, as we have noted a stationary and a rising titer with definite clinical improvement. As has been mentioned, in one group of patients there was a marked fluctuation in the agglutinin titer, although there was no apparent change in the clinical course. This was even apparent in a group of 6 patients tested at two day intervals for a period of two weeks.

Positive cutaneous reactions were more frequent and more marked in the group of patients with atrophic arthritis than in the control group but, as was explained earlier, the difference did not seem great enough to be worthy of consideration. Keefer, Myers and Oppel²² also reported comparisons of cutaneous with agglutination reactions in rheumatoid arthritis and rheumatic fever. Their use of the nucleoprotein of *Str. scarlatinae* may account for their greater percentage of positive reactions in these diseases as well as in acute respiratory diseases associated with *Str. haemolyticus*. We have noted a few large cutaneous reactions occurring within thirty minutes on several patients with atrophic arthritis, thus we agree with Keefer, Myers and Oppel that there may be an allergic factor.

In the group of patients given vaccine intravenously only a few showed a definite and constant rise in agglutinin titer. This rise was not necessarily associated with large doses, for in some cases in which the doses were as low as approximately 5,000,000 organisms it was marked and persistent, whereas in other cases in which the dosage reached 100,000,000 organisms and was continued for a long period no rise was noted. It may be of importance to mention again that all of these observations were made on patients treated intravenously, vaccine given subcutaneously or intramuscularly may have a different effect on the agglutinin titer.

²² Keefer, C. S., Myers, W. K., and Oppel, T. W. J. Clin. Investigation 12: 279, 1933.

Ordinarily a laboratory procedure is unnecessary in establishing a diagnosis of arthritis. Occasionally, in doubtful cases, when the facilities of a laboratory are available the AB 13 agglutinin titer may be an additional aid. After the diagnosis has been well established, the agglutinin titer has doubtful prognostic value because of the frequent extreme fluctuations of titer apparently unrelated to the clinical course. If this test is used to corroborate the diagnosis of early clinical stages, it should be applied under carefully controlled conditions in the laboratory and under the supervision of an experienced serologist. Accurate reading of the agglutination of streptococci presupposes a definite familiarity with the positive serologic picture produced by the particular organism involved. For this reason, the technic of the test does not lend itself to the conditions of an occasional isolated procedure in the laboratory.

CONCLUSIONS

1 Cecil's hemolytic streptococcus AB 13 shows a greater serologic selectivity for atrophic arthritis than for any other disease group studied, as evidenced by the percentage of positive reactions in high agglutinin titer.

2 The percentage of serums of patients with atrophic arthritis which contain agglutinins in high titer for AB 13 cannot be accounted for on the basis of (a) previous artificial immunization or (b) previous or concomitant streptococcal infections.

3 No other organism employed in this work was as selective as AB 13 for serums from patients with atrophic arthritis either in the height of the serum titer or in the frequency of positive agglutinin reactions.

4 No correlation was found between agglutinin titers and cutaneous reactions to vaccine of homologous organisms in the patients with atrophic arthritis.

5 Often within a short time a striking unexplained variation of agglutinin titers, not accounted for by clinical developments, occurs in patients untreated by vaccine.

6 In this study there was no regularity in the changes in the agglutinin titer as a result of vaccine therapy.

7 There is no apparent relationship between the variation in agglutinin titer and the clinical course.

8 A few patients seemed to be benefited by desensitization with vaccine. The improvement in other patients who received vaccine therapy may have been due to other factors impossible to control.

9 The AB 13 agglutinin titer has a definite but limited use as a diagnostic aid in arthritis.

ACTION OF DIURETIC DRUGS

I ACTION OF DIURETICS IN NORMAL PERSONS

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The various diuretics are of great clinical value in a wide variety of pathologic states, but the exact conditions which are most favorable for their action and the nature and mechanism of their action remain to a large extent obscure. One of the reasons for the unsatisfactory state of our knowledge is that the diseased states affected by the diuretic drugs vary from patient to patient, and, indeed, in the same patient. Consequently it is difficult to be certain as to what extent the changes following the administration of diuretics are due to those drugs and to what extent they result from spontaneous changes in the pathologic physiology of the conditions under investigation. Furthermore, complete studies of water and salt metabolism are so intricate that most of the investigations on the effect of diuretics are fragmentary and inconclusive.

It appeared desirable, therefore, to undertake a study of the various diuretics under conditions which are constant and readily reproducible. Previous work on the effect of extract of the posterior lobe of the pituitary gland on water and salt metabolism¹ has shown that such conditions can best be obtained with normal persons. For these reasons, the present studies, which form the basis of further observations in pathologic conditions with edema, were undertaken on normal subjects.

From the clinical point of view we have been interested in the character, magnitude and duration of the effect of the diuretic drugs, as

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From the Medical Research Laboratories and the medical service of the Beth Israel Hospital and the Department of Medicine, Harvard Medical School.

¹ Gargle, S L, Gilligan, D R, and Blumgart, H L. The Antidiuretic Effect of the Oxytocic and Pressor Principles of the Extract of the Posterior Lobe of the Pituitary, *New England J Med* **198** 169, 1928.

well as in the existence of any untoward reactions. From the physiologic point of view information has been sought in regard to the mechanism of action of these drugs. Four different diuretics have been administered, namely, salyrgan and merbaphen of the mercurial group, and metaphyllin (theophylline ethylenediamine) and theobromine sodium salicylate of the xanthine group.

PROCEDURE

The physical environment under which the action of the diuretics was studied was kept as constant as possible in order that the changes produced by the diuretics would not be obscured by relatively large fluctuations such as exist in the usual clinical environment. The subjects were placed in a metabolism room and confined to bed except for short periods each day. The room temperature was observed every four hours and did not exceed 78 F at any time.

The three normal adult men chosen as suitable for the study showed no evidence of renal or cardiac abnormalities. The subjects were well nourished, had normal basal metabolic rates and were intelligent and cooperative. E. W. previously had had acute nephritis, but he showed no evidence of renal damage at the time of the study.

Since the purpose of a diuretic is to remove abnormal deposits of body fluids without disturbing the normal composition of the remaining fluid matrix, it is essential that the drug should remove not only water but also the substances dissolved in the water. To learn to what extent the various common diuretics fulfil this essential requirement, we have studied all the electrolyte constituents of the urine which are present in important amounts in body fluids.

The observations reported in the literature on the effect of diuretics on water and mineral metabolism in man have generally been made on twenty-four hour specimens of urine. Our previous studies¹ of the effect of extract of the posterior lobe of the pituitary have demonstrated the necessity of collecting the urine at frequent stated intervals during the twenty-four hour period in order to evaluate the effect of this drug accurately. Marked changes in water and salt metabolism caused by a single dose of pituitary extract were followed in a few hours by equally marked changes in the opposite direction, so that no effects were obvious in the amount of urine collected in twenty-four hours. It was considered of the utmost importance, therefore, in studying the effect of the diuretics on the water and salt metabolism, to divide the observations into short periods of time, as they are presented in table 1.

The study of specimens of urine collected at repeated intervals during the day permits a more accurate estimation of the duration of the diuretic effect, and also enables one to learn whether the general nature of the diuresis is the same in the initial as in the later periods.

A carefully weighed neutral diet (table 2), adequate in all respects, was given at specified times each day, and on no occasion was food returned uneaten. The subjects received the same articles of food every day, the three meals differing from each other but being exactly the same from day to day. This diet was so designed as to permit its use in other studies on patients with nephritis and cardiovascular disease. The diet was planned to contain small amounts of sodium and chloride, and the necessary requirements were met by adding salt in the form of chemically pure sodium chloride, thereby reducing variations in the intake of salt to a minimum.

TABLE 1—Daily Schedule

7 00 a m	Void
7 30 a m	Breakfast
9 30 a m	Void
9 30 a m	333 cc water
12 00 noon	Void
12 00 noon	Dinner
2 00 p m	Void
2 30 p m	333 cc water
4 30 p m	Void
4 30 p m	Supper
6 30 p m	Void
7 30 p m	334 cc water
9 00 p m	Void

TABLE 2—Total Daily Dietary Intake Used Throughout the Studies

Subject	Protein, Gm	Fat, Gm	Carbohydrate, Gm	Calories	Chloride		Sodium		Potassium		Calcium, Calculated, M Eq	Magnesium, Calculated, M Eq	Phosphorus, Calculated, M Eq	Sulphur, Calculated, M Eq	Water	
					Calculated, M Eq	Analyzed, M Eq	Calculated, M Eq	Analyzed, M Eq	Calculated, M Eq	Analyzed, M Eq					Calculated, Gm	Analyzed, Gm
S. D.	66	105	254	2,230	69	82	75	75	69	57	24	17	34	36	1,521	1,466
S. A.	66	80	224	1,880	69	82	75	75	69	57	24	17	34	36	1,521	1,466
E. W.	46	69	141	1,320	62	68	101	100	30	28	19	9	37	40	1,080	1,005

Exact duplicates of the diet were analyzed chemically on several occasions to make certain of the actual total intake of the most important inorganic constituents. The values used for the calculation of this diet were obtained in part from analyses made by Aub,² and in part from Sherman's tables.³ The calculated water contents were obtained from circulars from the United States Department of Agriculture.⁴ The analytic values for the potassium and chloride contents

2 Aub, J. C. Personal communication to the authors.
3 Sherman, H. C. Chemistry of Food and Nutrition, New York, The Macmillan Company, 1928.
4 United States Department of Agriculture Circulars nos. 50 (Dec. 1928), 146 (Jan. 1931) and 389 (July 1926).

of the diets differed somewhat from the calculated values (table 2). The constancy of the diet was demonstrated by the close agreement of the results of analyses made during different periods of the study. In addition to the water supplied in the diet, 1 liter of water divided into three equal portions was given to each subject at specified times during the day (table 1).

The daily schedule given in table 1 was adhered to strictly. No medication, except the diuretics studied, was given. No quantitative studies were made until the subjects had been on the metabolic regimen for a week or more. Preliminary measurements were then made until the subjects were in satisfactory equilibrium with the conditions of the study. Measurements of the volume and of the various constituents of each specimen of urine were then made for several days before a diuretic was administered, to learn the extent of the spontaneous variations under the fixed conditions of the experiment.

METHODS

The specimens of urine were collected directly in bottles containing toluene as a preservative. The ammonia content and titratable acidity were determined when specimens were fresh. The chloride content was also usually determined within twenty-four hours after voiding, and a small amount of concentrated hydrochloric acid was then added to each specimen as an additional preservative, and to prevent the precipitation of alkaline phosphates.

Stools were demarcated by the oral administration of 1 Gm of ashless lamp-black charcoal at the beginning and at the end of each period of observation. They were weighed shortly after passage to prevent a loss of water by evaporation.

Body weights were determined daily, and at additional times when desired, by means of a beam balance which gave results accurate to approximately 1 Gm.

The chemical methods used for the analyses of urine were as follows: ammonia, Van Slyke and Cullen,⁵ chloride, Folin,⁶ inorganic phosphorus, Fiske and Subbarow,⁷ inorganic sulphate, Fiske,⁸ potassium, Fiske and Litarczek,⁹ sodium, Butler and Tuthill,¹⁰ titratable acidity minus carbon dioxide by adding 5 cc of one-tenth normal hydrochloric acid to 25 cc of urine, blowing off carbon dioxide and titrating to pH 7.38 with one-tenth normal sodium hydroxide, using phenol-

5 Van Slyke, D. D., and Cullen, G. E. A Permanent Preparation of Urease and Its Use in the Determination of Urea, *J. Biol. Chem.* **19** 211, 1914, The Determination of Urea by the Urease Method, *ibid.* **24** 117, 1916.

6 Folin, O. Simplified Chlorid Determination in Laboratory Manual of Biological Chemistry, ed. 4, New York, D. Appleton and Company, 1926, p. 167.

7 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66** 375, 1925.

8 Fiske, C. H. The Determination of Inorganic Sulphate, Total Sulphate and Total Sulphur in Urine by the Benzidine Method, *J. Biol. Chem.* **47** 59, 1921.

9 Fiske, C. H., and Litarczek, G. Unpublished data.

10 Butler, A. M., and Tuthill, Elizabeth. An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, *J. Biol. Chem.* **93** 171, 1931.

sulphonphthalein as an indicator and a standard phosphate buffer for color comparison, a modification of the method of Henderson and Palmer,¹¹ calcium, Fiske and Logan,¹² total nitrogen, Folin,¹³ urea clearance, Moller, McIntosh and Van Slyke¹⁴ and McIntosh, Moller and Van Slyke,¹⁵ and creatinine, Folin.¹⁶ The same methods, with slight modifications when necessary, were used for analyses of stools. The stools were ashed by the nitric acid wet ash method. The results of the analyses of the various constituents in the individual specimens of urine were checked by comparison with the results found for a representative twenty-four hour amount obtained by combining 10 per cent of the volume of each individual specimen. The analyses of stools were made in duplicate on the ashed extracts.

The serum constituents were determined by the following procedures: chloride, Wilson and Ball,¹⁷ sodium, Rourke,¹⁸ specific gravity (bottles containing 5 cc were used), Moore and Van Slyke,¹⁹ creatinine, Folin,²⁰ and protein, Dyer.²¹ All the analyses of serum were made in duplicate. The accuracy of the chemical methods employed in all the studies was confirmed by analyzing known solutions at frequent intervals during the course of the investigation.

11 Henderson, L J, and Palmer, W W. On the Several Factors of Acid Excretion, *J Biol Chem* **17** 305, 1914

12 Fiske, C H, and Logan, M A. The Determination of Calcium by Alkalimetric Titration. II. The Precipitation of Calcium in the Presence of Magnesium, Phosphate and Sulphate, with Applications to the Analysis of Urine, *J Biol Chem* **93** 211, 1931

13 Folin, O. Total Nitrogen Determination in Urine by Direct Nesslerization, in *Laboratory Manual of Biological Chemistry*, New York, D Appleton and Company, 1926

14 Moller, E, McIntosh, J F, and Van Slyke, D D. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J Clin Investigation* **6** 427, 1928

15 McIntosh, J F, Moller, E, and Van Slyke, D D. Studies of Urea Excretion. III. The Influence of Body Size on Urea Output, *J Clin Investigation* **6** 467, 1928

16 Folin, O. On the Determination of Creatinine and Creatine in Urine, *J Biol Chem* **17** 469, 1914

17 Wilson, D W, and Ball, E G. A Study of the Estimation of Chloride in Blood and Serum, *J Biol Chem* **79** 221, 1928

18 Rourke, M D. The Determination of the Sodium Content of Small Amounts of Serum or Heparinized Plasma by the Iodometric Method, *J Biol Chem* **78** 337, 1928

19 Moore, N S, and Van Slyke, D D. The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, *J Clin Investigation* **8** 337, 1930

20 Folin, O. On the Determination of Creatinine and Creatine in Blood, Milk, and Tissues, *J Biol Chem* **17** 475, 1914

21 Dyer, B. Kjeldahl's Method for the Determination of Nitrogen, *J Chem Soc, London* **47** 811, 1895

The rates of glomerular filtration were measured by the method of Rehberg,²² slightly modified, in that no creatinine was fed, and the creatinine contents of the serum and urine were determined by the methods of Folin²³

Owing to the many extraneous factors which affect water and salt metabolism, even under the rigidly controlled conditions of this study, the urinary outputs of water and inorganic salts showed variations for single periods, which were, at times, considerable. For this reason, the average urinary findings for the individual periods of the several control days, before the diuretic was administered, were used as the basis of comparison. In this way a base line was established, according to which the diuretic effect of the drug administered could be gaged more accurately.

In accord with these considerations the net quantitative effect of the diuretics was measured by the increases above or the decreases below the average excretion during corresponding periods on the control days immediately preceding the medication. In presenting the results, the amounts above or the amounts below the corresponding average figures of the original preliminary control periods have been charted (figs 1 to 9), rather than the total amounts excreted.

The data have also been analyzed to gain information as to the source of the increased output of water and inorganic salts following the administration of the diuretics. The measurements of the urine include the constituents which occur in important amounts in body fluids, namely chloride, sodium, potassium and calcium. In addition to these constituents, the amounts of other substances in the urine, the excretion of which is important in maintaining the constancy of the acid-base equilibrium of the body, have been determined. These include inorganic phosphate, inorganic sulphate, ammonia, titratable acid (minus carbon dioxide) and total nitrogen.

RESULTS

In the following presentation of results, the data for the water, sodium, chloride, potassium and calcium in the urine will be discussed for each experiment. The findings in regard to the urinary excretion of inorganic phosphate, inorganic sulphate and ammonia and the titratable acidity and specific gravity of the urine will be discussed together later.

Effect of Merbaphen on S D—The administration of 2 cc of merbaphen intravenously caused an increase in the volume of urine (table 3) during the first seven hours after the injection of the drug, accompanied by a conspicuously increased excretion of sodium, chloride,

²² Rehberg, P. B. Studies on Kidney Function. I. The Rate of Filtration and Reabsorption in the Human Kidney, *Biochem J* 20:447, 1926.

²³ Folin (footnotes 16 and 20).

potassium and calcium (fig 1) There was a relatively constant relationship between the increases in the excretion of chloride, sodium and calcium during the different periods of diuresis (fig 1) This indicates that the diuresis was not primarily a diuresis of chloride or of any other single constituent The increase in the excretion of potassium appeared somewhat later and persisted after the period of diuresis of water, sodium, chloride and calcium Immediately following the increased

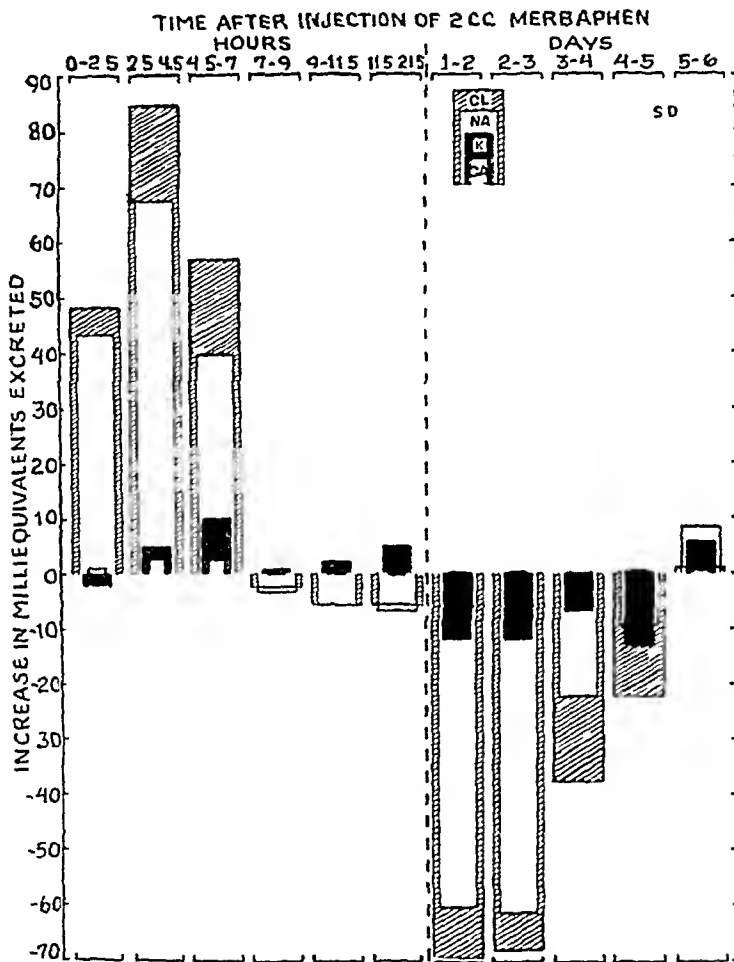


Fig 1—Net effect of the intravenous administration of 2 cc of merbaphen on the urinary excretion and subsequent retention of chloride, sodium, potassium and calcium in S D In this and in all the following figures the amounts above or below the average values for the corresponding control periods have been charted The figures represent, therefore, the net effect of the action of the drug on those constituents of the body The effect of the diuretics on the excretion of inorganic phosphate, inorganic sulphate and ammonia and on the titratable acidity was much less significant and has not been charted

excretion there was a compensatory diminution in the output of these substances lasting for four days This period of retention restored to the body the substances which had been lost during the period of diuresis The restraining factor which prevented a more rapid

restoration of the lost body fluid was evidently the restricted intake of sodium chloride. This fact is demonstrated by the failure to retain available water in the absence of corresponding amounts of salt, for the volume of urine was relatively great in view of the nearly complete absence of sodium and chloride in the urine during the first two days following the diuresis (table 3). Furthermore, as evident from the divided specimens of urine on the first day following the diuresis (table 3), there was almost complete retention of available sodium and chloride during the periods immediately following meals, as well as in the intervals.

The studies of Gamble, Ross and Tisdall²⁴ have added considerable significance to measurements of the excretion of sodium and potassium. Potassium is the predominant base in cells,²⁵ while sodium predominates in blood plasma and other extracellular fluids. In edema fluid, which may be taken as an example of extracellular fluid, sodium and potassium are present in concentrations of approximately 145 and 4 milliequivalents per liter of water, respectively, according to results obtained by workers in our laboratory²⁶ and by Greene and his co-workers.²⁷ According to Peters,²⁸ the base of cells is probably almost entirely potassium. The concentration of total base throughout the body fluids is approximately the same. It may be assumed, therefore, that the potassium of cell water is approximately 160 milliequivalents per liter.

The increase in the amount of sodium excreted by the subject S. D. during the seven hours of diuresis following the administration of 2 cc of merbaphen was 3.5 Gm., or approximately 150 milliequivalents, the increase in the amount of potassium excreted simultaneously was 0.5 Gm., or approximately 13 milliequivalents. Applying these data to the aforementioned considerations, it is apparent that the amount of sodium excreted during the diuresis, namely 150 milliequivalents, is equivalent to the sodium content of 1,030 cc ($\frac{150}{145} \times 1,000$) of interstitial fluid. The potassium content of this amount of interstitial fluid would be approximately 4 milliequivalents. The remaining 9 milliequivalents of potassium excreted during the diuresis was presumably

24 Gamble, J. L., Ross, G. S., and Tisdall, F. F. Metabolism of Fixed Base During Fasting, *J. Biol. Chem.* **57** 633, 1923.

25 Katz, J. Die mineralischen Bestandtheile des Muskelfleisches, *Arch. f. d. ges. Physiol.* **63** 1, 1896.

26 Gilligan, D., Rourke, Volk, M. C., and Blumgart, H. L. Observations on the Chemical and Physical Relation Between Blood Serum and Body Fluids. I. The Nature of Edema Fluids and Evidence Regarding the Mechanism of Edema Formation, *J. Clin. Investigation* **13** 365, 1934.

27 Greene, C. H., Bollman, J. L., Keith, N. M., and Wakefield, E. G. The Distribution of Electrolytes Between Serum and Transudates, *J. Biol. Chem.* **91**, 203, 1931.

28 Peters, J. P. Personal communication to the authors.

TABLE 3—Effect of Diuretics on the Urinary Excretion of S₂U

Date, 1931	Medication	Time of Voiding	Volume, Cc	Specific Gravity	Chloride, M Eq	Sodium, M Eq	Potas- sium, M Eq	Calcium, M Eq	Ammonia Nitrogen, M Eq	Titratable Acidity Minus Carbon Dioxide, M Eq	Inorganic Phos- phorus,* M Eq	Inorganic Sulphate Sulphur, M Eq	Total Nitrogen, Gm
5/19		9 30 a m	86	1.025	122	103	72		27	+26	46		
		12 00 noon	90	1.020	152	72	115		26	+19	33		
		2 00 p m	150	1.012	97	93	53		23	+42	59		
		4 30 p m	314	1.007	113	120	41		37	+34	71		
		6 30 p m	204	1.005	78	60	21		34	+32	38		
		9 00 p m	341	1.004	78	98	21		36	+23	45		
		7 00 a m	156	1.024	66	84	96		106	+13	118		
		Total	1,341	1.011	706	630	419	52	239	+188	410		94
5/20		9 30 a m	69	1.025	93	75	60		33	+49	36	39	
		12 00 noon	63	1.027	103	41	95		31	+24	26	33	
		2 00 p m	99	1.026	180	152	87		25	+38	40	40	
		4 30 p m	61	1.028	85	88	71		15	+12	29	34	
		6 30 p m	101	1.017	82	81	46		35	+32	46	37	
		9 00 p m	397	1.005	92	134	26		36	+19	42	35	
		7 00 a m	151	1.026	68	91	93		112	+87	103	107	
		Total	941	1.018	709	662	478	58	287	+262	352	325	87
5/21		9 30 a m	72	1.023	107	91	56	12	28	+24	35	37	
		12 00 noon	140	1.017	272	200	138	10	29	+32	31	42	
		2 00 p m	145	1.015	146	164	04	07	20	+64	64	27	
		4 30 p m	303	1.005	86	97	48	05	30	+10	36	24	
		6 30 p m	166	1.007	89	85	32	00	41	+20	35	30	
		9 00 p m	342	1.003	51	82	31	04	40	+15	33	40	
		7 00 a m	167	1.007	50	55	100	06	120	+84	103	109	
		Total	1,333	1.012	801	772	469	50	308	+185	337	309	78
5/22	Merbaphen, 2 cc intravenously at 9 30 a m	9 30 a m †	76	1.024	107	90	03	12	29	+15	39	38	
		12 00 noon	355	1.019	657	519	95	19	59	+28	19	25	
		2 00 p m	482	1.007	991	809	115	33	43	+30	37	22	
		4 30 p m	625	1.006	662	495	153	30	50	+17	26	32	
		6 30 p m	81	1.015	58	11	41	05	34	+27	46	21	
		9 00 p m	321	1.005	15				130	+100	148	118	
		7 00 a m	151	1.024	07	08	145	03					
		Total	1,934	1.008	2,197				389		359	288	76
5/23		9 30 a m	58	1.029	07	08	46	10	29	+35	49	44	
		12 00 noon	210	1.008	08	10	36	11	41	+13	30	29	
		2 00 p m	82	1.022	04	09	39	00	33	+33	64	30	
		4 30 p m	236	1.009	07	12	51	06	47	+30	30	34	
		6 30 p m	162	1.008	04	07	28	05	37	+21	62	27	
		9 00 p m	260	1.005	07	28	39	06	50	+37	63	44	
		7 00 a m	150	1.023	06	09	97	09	134	+82	118	104	
		Total	1,258	1.010	43	83	330	53	387	+250	428	312	85
5/24		Total	930	1.010	57	75	335	55	330	+202	377		80
5/25		Total	1,026	1.011	359	464	387	49	233	+140	303		83
5/26		Total	1,252	1.012	510	792	324	57	280	+126	375		85
5/27		Total	1,060	1.014	749	771	512	58	326	+228	409		99

6/ 6	9 30 a m	93	1 020	14 9	11 6	8 2						4 5
	12 00 noon	207	1 007	15 9	9 4	11 4						1 7
	2 00 p m	57	1 025	7 0	7 8	3 8						4 5
	4 30 p m	275	1 006	10 3	5 2	8 8						5 3
	6 30 p m	80	1 017	5 9	6 8	2 6						5 2
	9 00 p m	314	1 003	9 6	14 9	3 6						5 5
	7 00 a m	146	1 022	6 2	8 0	9 0						12 2
	Total	1,172	1 012	69 8	63 7	47 4	5 5	28 9	+24 6		38 9	8 5
6/ 7	9 30 a m	53	1 030	6 1	3 4	5 2					4 4	3 7
	12 00 noon	105	1 015	14 7	10 0	10 2					2 7	2 7
	2 00 p m	363	1 005	17 2	16 1	10 7					7 1	2 4
	4 30 p m	152	1 007	4 4	2 9	5 0					2 3	2 3
	6 30 p m	211	1 004	6 3	8 4	4 1					5 0	2 8
	9 00 p m	454	1 001	9 1	12 2	4 2					3 9	3 1
	7 00 a m	219	1 013	14 0	15 7	10 4					11 5	12 6
	Total	1,557	1 010	71 8	68 7	49 8		30 7	+26 7		38 8	8 9
6/ 8	9 30 a m	63	1 027	7 1	5 9	6 7	1 0	2 7			4 9	3 5
	12 00 noon	146	1 016	15 0	6 9	14 8	0 6	2 9			4 9	3 1
	2 00 p m	185	1 012	4 4	8 4	6 2	0 8	3 4			10 6	3 9
	4 30 p m	130	1 011	3 5	3 5	3 8	0 6	3 1			3 6	1 9
	6 30 p m	373	1 003	4 7	5 6	2 4	0 7	3 4			3 1	1 9
	9 00 p m	610	1 004	12 2	23 2	6 8	0 7	2 4			5 5	4 0
	7 00 a m	206	1 019	13 8	23 2	9 2	1 0	9 5			11 9	9 7
	Total	1,713	1 011	60 7	76 7	49 9	5 3	27 4	+27 4		44 5	8 6
6/ 9	9 30 a m	132	1 021	19 9	15 9	8 5	1 1	2 9			5 3	4 0
	12 00 noon	562	1 011	61 1	53 3	17 8	2 7	2 5			4 1	3 5
	2 00 p m	400	1 014	43 6	47 7	9 4	1 9	2 0			10 1	3 4
	4 30 p m	526	1 006	18 5	21 0	9 4	1 0	1 6			4 8	2 2
	6 30 p m	114	1 015	9 0	10 0	3 0	0 4	2 8			5 3	2 9
	9 00 p m	435	1 006	12 2	18 0	4 1	0 8	3 1			8 4	5 0
	7 00 a m	140	1 026	3 4	6 6	13 0	0 4	9 5			12 8	10 6
	Total	2,309	1 010	167 7	172 5	65 2	8 3	24 4			50 8	9 6
6/10	Total	753	1 010	13 2	15 4	29 5	3 8	30 2			33 1	9 4
6/11	Total	1,018	1 014	28 0	17 6	34 3	5 0	32 6			40 9	9 5
6/12	Total	1,275	1 012	44 1	35 3	43 7	5 8	36 5			44 9	9 2
6/13	Total	2,104	1 010	111 5	100 6	57 0		31 9	+11 4		44 2	9 7

* The valence was assumed to be 18
+ Some of the urine was lost for this period, and the figures given are calculated from results on preceding days

TABLE 3—Effect of Diuretics on the Urinary Excretion of S D—Concluded

Date, 1931	Medication	Time of Voiding	Volume, Cc	Specific Gravity	Chloride, M Eq	Sodium M Fq	Potas- sium, M Eq	Calcium, M Eq	Ammonia Nitrogen, M Fq	Titratable Acidity Minus Carbon Dioxide, M Eq	Inorganic Phosphate Phos- phorus,* M Fq	Inorganic Sulphur, M Eq	Total Nitrogen, Gm
6/28		9 30 a m	86	1.019	6.8	5.5					4.7		
		12 00 noon	241	1.009	20.1	12.4					3.3		
		2 00 p m	333	1.008	19.1	20.8					7.5		
		4 30 p m	249	1.006	8.3	10.8					3.9		
		6 30 p m	340	1.002	4.8	5.8					3.7		
		9 00 p m	161	1.011	7.5	9.4					5.3		
		7 00 a m	139	1.020	3.1	2.4					11.4		
		Total	1,569	1.007	69.5	67.1	45.0		26.2	+11.2	39.8		7.9
6/29		9 30 a m	66	1.023	8.7	6.8					3.4		
		12 00 noon	127	1.017	17.2	9.2					3.1		
		2 00 p m	478	1.006	17.8	16.1					6.2		
		4 30 p m	453	1.007	22.6	23.6					4.9		
		6 30 p m	208	1.007	9.8	11.1					3.6		
		9 00 p m	118	1.011	8.1	10.2					3.7		
		7 00 a m	147	1.021	2.8	1.1					12.2		
		Total	1,599	1.008	87.0	80.4	42.8		28.7	+11.1	37.1		8.1
6/30		9 30 a m	51	1.025	3.9	3.2			3.4		4.0		
		12 00 noon	312	1.007	16.7	8.2			4.0		4.1		
		2 00 p m	245	1.008	10.3	11.0			2.8		6.3		
		4 30 p m	395	1.005	14.2	12.9			2.9		4.4		
		6 30 p m	435	1.004	7.7	7.3			3.3		4.2		
		9 00 p m	157	1.011	7.5	11.4			4.3		4.1		
		7 00 a m	159	1.024	3.1	2.4			13.2		16.1		
		Total	1,754	1.011	61.4	56.1	52.0		33.9	+20.1	43.5		8.6
7/1	Theobromine sodium salicylate, 3 Gm by mouth at 9 30 a m	9 30 a m	50	1.028	1.0	1.2			2.0		4.5		
		12 00 noon	404	1.008	35.1	27.3			3.0		4.0		
		2 00 p m	135	1.020	11.8	15.3			2.0		6.6		
		4 30 p m	180	1.010	5.8	5.9					3.9		
		6 30 p m	162	1.006	1.8	1.5			4.4		1.1		
		9 00 p m	475	1.002	1.9	2.9					6.2		
		7 00 a m	207	1.016	1.6	1.4					13.8		
		Total	1,613	1.009	65.3	53.5	58.0		33.2	+10.8	43.1		8.9
7/2		Total	1,763	1.008	75.6	53.8	41.2		29.1	+13.1	36.1		8.2
7/3		Total	1,808	1.008	67.1	59.0	36.1		28.2		36.3		7.4

* The valence was assumed to be 18

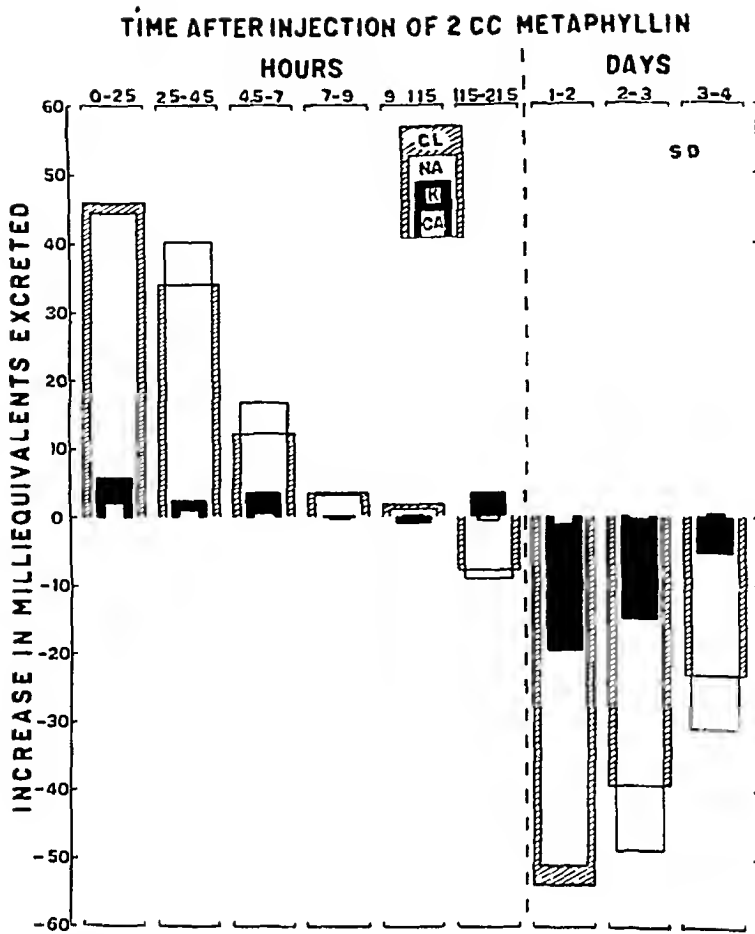


Fig 2—Net effect of the intravenous administration of 2 cc of metaphyllin on the urinary excretion and subsequent retention of chloride, sodium, potassium and calcium in S D

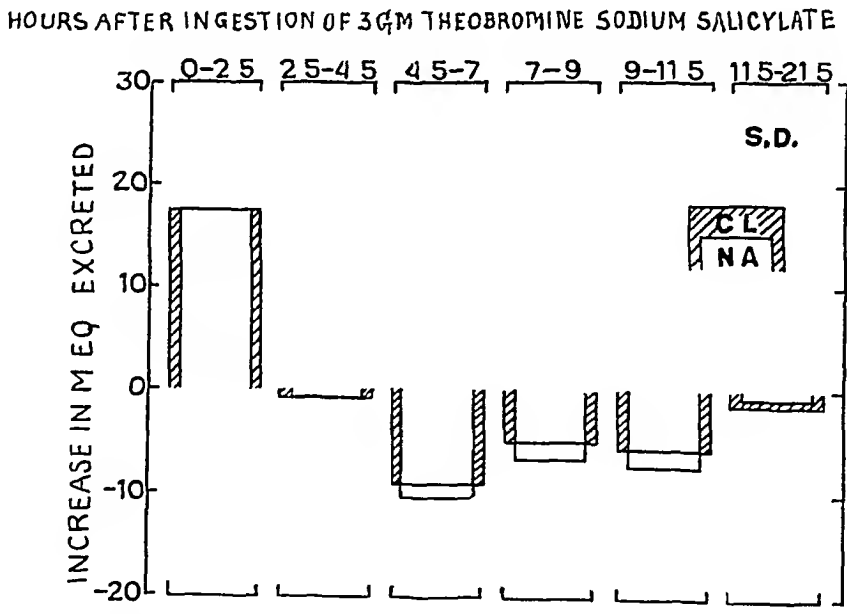


Fig 3—Net effect of the oral administration of 3 Gm of theobromine sodium salicylate on the urinary excretion and subsequent retention of chloride and sodium in S D

derived from intracellular fluid. Since the potassium content of cell water is approximately 160 milliequivalents per liter, it is evident that little intracellular fluid was excreted by this subject following the administration of 2 cc of merbaphen. Calculations of such small amounts inevitably contain a large inherent error, but it is interesting to note that the calculations for the excretion of potassium indicate the loss of approximately 60 cc of cell water.

These calculations, on the basis of the amounts of sodium and potassium excreted, indicate that in this subject the predominant effect of merbaphen was a loss of extracellular fluid. The total calculated amount of water lost from the body, extracellular plus intracellular, was 1,090 cc. One might, therefore, expect an increase in the urinary volume and a net decrease in body weight of approximately the same amount, the observed increase in the volume of urine excreted during the diuretic period was 907 cc., and the net loss in weight²⁹ was 1,030 Gm during the same period. There was considerable variation in the urinary volume during the corresponding periods of the three control days. With these considerations in mind, the correspondence between the calculated loss of body water and the increase in the urinary volume is satisfactory and supports the interpretation of the excretion of sodium and potassium during this diuresis in terms of loss of body fluid.

The minute amounts of calcium excreted in the urine during the control periods were increased several hundred per cent during the diuresis following merbaphen. The increased excretion of calcium during the diuretic period was, in this instance, 6 milliequivalents. Since the calcium content of normal interstitial fluid may be considered to be approximately 4 milliequivalents per liter,³⁰ and the diuresis in this instance was approximately 1 liter, it appears that the calcium excreted was derived mainly from the extracellular body fluids lost during the diuresis.

The increase in the amount of chloride excreted during the diuresis was approximately 68 Gm or 190 milliequivalents. The total loss of body fluid during the diuresis, as calculated from the increased excretion of base, was 1,090 cc. If one assumes the chloride to be 110 milli-

²⁹ The "net loss in body weight" refers to the loss of weight directly attributable to the effect of the drug, the factors of intake of food and water, blood drawn, stools excreted and average control urinary outputs and insensible losses of weight having been utilized in obtaining this value.

³⁰ Loeb, R. F., Atchley, D. W., and Palmer, W. W. On the Equilibrium Condition Between Blood Serum and Serous Cavity Fluids, *J. Gen. Physiol.* 4: 591, 1922. Gilligan, Volk and Blumgart.²⁶ Greene, Bollman, Keith and Wakefield.²⁷

equivalents per liter of water in body fluid³¹ the excretion of chloride, to correspond to the excretion of base, was about 120 milliequivalents. This leaves an excess of 70 milliequivalents of chloride excreted which cannot be accounted for on the basis of loss of body fluid. Likewise, during the periods of retention following the diuresis (fig 1) the chloride retained was in excess of the base retained. These findings will be discussed later.

Effect of 2 cc of Metaphyllin Intravenously on S D—To compare the effect of the purine diuretics with that of the mercurial diuretics in the same subject, 2 cc of metaphyllin³² was injected intravenously. The intravenous method of administration was employed in order to render the results as comparable as possible. Metaphyllin caused a marked increase in the urinary output (table 3) and in the amounts of sodium, chloride, potassium and calcium excreted (fig 2). The diuresis following the administration of metaphyllin lasted approximately nine hours. The periods of marked diuresis following metaphyllin coincided with those following merbaphen. The general relation between the various constituents excreted during the diuresis was similar in each period of marked diuresis. The period of retention following metaphyllin persisted for a somewhat shorter time (table 3), this is related to the fact that metaphyllin caused a smaller loss of constituents of the body fluids, consequently, under the fixed regimen of the study, a shorter period was required to restore these smaller amounts.

The increased amount of sodium excreted during the diuresis was approximately 2.3 Gm or 100 milliequivalents, that of potassium, 0.46 Gm or 12 milliequivalents, and that of calcium, 0.074 Gm or 3.7 milliequivalents. According to the considerations previously discussed, calculations based on the increased amounts of sodium excreted gave a value of 690 cc ($\frac{100 \text{ m eq}}{145 \text{ m eq}} \times 1,000 \text{ cc}$) for the extracellular fluid lost. The potassium content of this amount of extracellular fluid is approximately 3 milliequivalents. The remaining 9 milliequivalents of potassium excreted was presumably derived from intracellular fluid, as stated, and indicates the loss of approximately 60 cc of cell water. Of the 3.7 milliequivalents of excess calcium excreted during the diuresis, approximately 2.8 milliequivalents can be accounted for on the basis of the calculated loss of water from the interstitial body fluids. The increase in the amount of chloride excreted during this diuresis was approxi-

31 This value may be assumed to be approximately correct for interstitial body water. Intracellular body water has a considerably smaller chloride concentration. Since the diuresis in this and in the following studies was mainly interstitial, this value serves as a close approximation. Footnote 30.

32 Two cubic centimeters of metaphyllin was diluted with 8 cc of physiologic solution of sodium chloride when given intravenously.

mately 3.4 Gm or 96 milliequivalents. According to the assumptions previously discussed, the amount of chloride excreted, to correspond to the amount of base excreted on the basis of body fluid contents, was 83 milliequivalents. The total calculated loss of body fluid during the nine hours of diuresis was 750 cc. Considering the inherent variations in the volume of urine on control days, this value compares satisfactorily with the observed increase of 874 cc in the volume of urine and the net loss of body weight of 813 Gm during this period. In S. D. the purine diuretic, metaphyllin, like merbaphen, exerted its effect predominantly on the extracellular fluids, the intracellular fluid compartment being affected to only a slight degree.

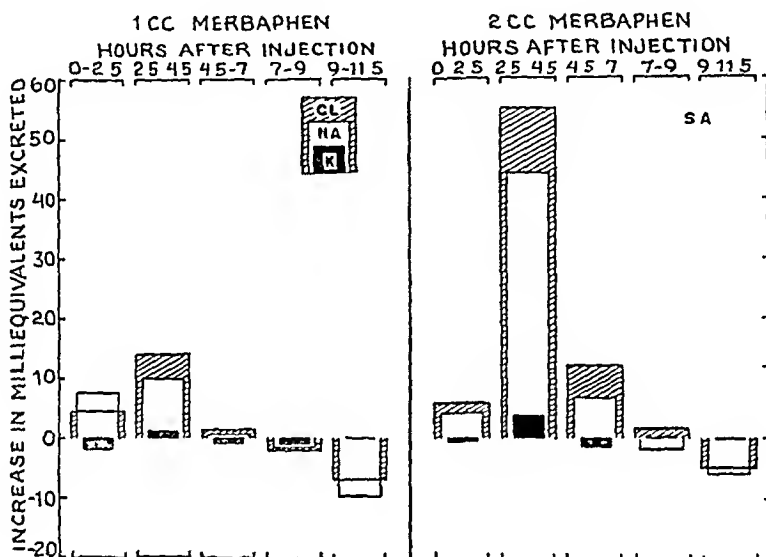


Fig 4—Net effect of the intravenous administration of 1 and 2 cc of merbaphen on the urinary excretion of chloride, sodium and potassium in S. A.

Effect of 3 Gm of Theobromine Sodium Salicylate Orally on S. D.—The oral administration of 3 Gm of theobromine sodium salicylate caused a transitory diuresis (table 3) evident only in the first specimen of urine, which was voided two and a half hours after the drug had been given. The increased amounts of the inorganic ions excreted (fig 3) were too small to permit making calculations of significance in regard to losses of body fluid. It should be noted that the retention of substances during the latter part of the twenty-four hour period during which the drug was given compensated fully for the amounts of chloride, sodium and water excreted in excess of the usual amounts. The total values for sodium, chloride and volume for the twenty-four hour period were consequently the same as on the days when no medication was given. The findings of some investigators who failed to observe any diuretic

effects after the administration of this drug³³ are readily understood, in view of the brief diuresis and the immediately ensuing retention observed by us, since these investigators measured only the total twenty-four hour specimens of urine

Effect of 1 and 2 cc of Merbaphen Intravenously on S A—To evaluate the effect of different doses of the same drug, 1 and 2 cc of merbaphen were given to another subject (S A). An increase in the volume of the urine and in the amounts of sodium and chloride excreted occurred immediately after the intravenous administration of both 1 and 2 cc of merbaphen (table 4). The relation of the increases in the various constituents of the urine (fig 4) was similar to that noted in S D following 2 cc of merbaphen, but much less striking. Two cubic centimeters of merbaphen was approximately three times as effective

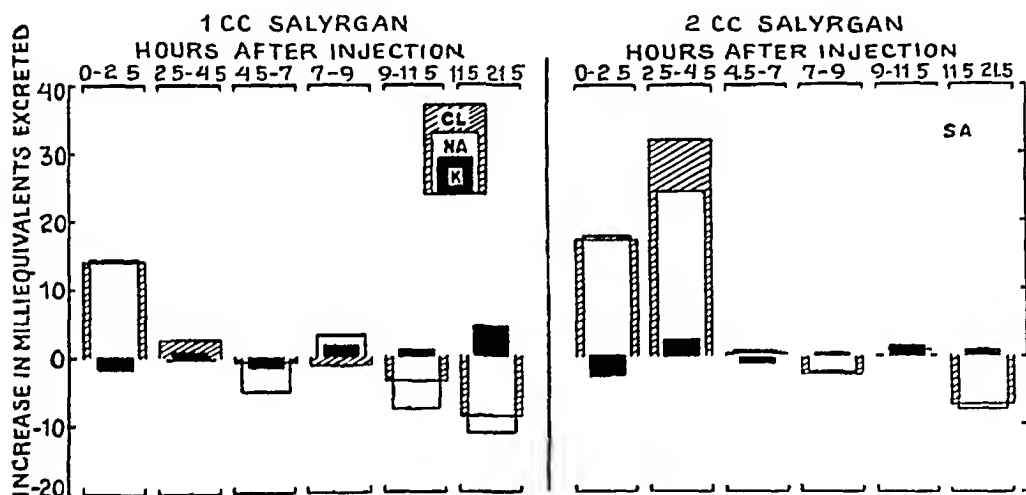


Fig 5—Net effect of the intravenous administration of 1 and 2 cc of salyrgan on the urinary excretion of chloride, sodium and potassium in S A

as 1 cc, and the duration of the diuresis was somewhat longer. In this subject the urinary changes following merbaphen were not sufficiently great to warrant calculations of the amounts of intracellular and extracellular fluids represented by the increases in the urinary base, but the predominant loss of sodium indicates that the interstitial fluid compartment was drawn on mainly.

Effect of 1 and 2 cc of Salyrgan Intravenously on S A—In this subject the diuretic effect of 2 cc of salyrgan was somewhat less than that of 2 cc of merbaphen (table 4). A twofold increase in the dose of salyrgan, i e., from 1 to 2 cc, caused approximately a twofold increase in the duration of the diuresis and a threefold increase in the total output of water, sodium and chloride (fig 5). The excretion of

33 Grossmann, M, and Sandor, J. Zur klinischen Pharmakologie der Diuretika. I. Die Puringruppe, Wien klin Wchnschr 38 405, 1925

TABLE 4—Effect of Diuretics on the Urinary Excretion of S A

Date, 1931	Medication	Time of Voiding	Volume, Cc	Specific Gravity	Chloride, M Lq	Sodium, M Lq	Potas- sium, M Eq	Calcium, M Eq	Ammonia Nitrogen, M Lq	Titratable Acidity Minus Carbon Dioxide, M Eq	Inorganic Phosphorus, M Eq	Inorganic Sulphate, M Eq	Total Nitrogen, Gm
4/ 3		9 30 a m	72	1.024	8.4	5.5	6.6		2.9	+ 1.1	2.7		
		12 00 noon	223	1.012	17.0	10.4	11.4		2.4	— 2.1	1.3		
		2 00 p m	94	1.016	7.7	6.2	3.7		2.7	+ 2.0	3.2		
		4 30 p m	272	1.007	6.7	6.6	5.6		4.0	+ 1.3	3.7		
		6 30 p m	150	1.017	3.9	2.7	3.9		6.5	+ 2.7	4.1		
		9 00 p m	740	1.008	14.2	18.0	5.4		2.0	— 1.5	3.7		
		7 00 a m	256	1.022	7.5	14.9	9.7			+ 6.3	11.1		
	Total		1,807	1.013	65.4	64.3	46.2			+ 9.8	29.8		
4/ 6		9 30 a m	98	1.015	8.6	5.4	9.2		5.8	+ 0.7	3.5		
		12 00 noon	330	1.005	18.2	10.9	12.2		0.4	— 2.4	1.7		
		2 00 p m	75	1.016	7.9	5.9	1.9		2.0	+ 1.9	3.1		
		4 30 p m	296	1.005	5.9	3.4	7.5		5.4	+ 2.1	3.7		
		6 30 p m	192	1.007	3.5	2.5	5.5		2.1	+ 2.7	4.3		
		9 00 p m †	207	1.008	5.8	6.7	5.4		2.2	+ 2.2	4.0		
		7 00 a m	512	1.009	10.3	7.4	12.9		11.2	+ 6.8	11.7		
	Total		1,710	1.010	60.2	42.2	57.6		29.1	+ 14.0	32.0		
4/ 7	Morbaphen, 1 cc intravenously at 9 30 a m	9 30 a m	88	1.017	7.9	4.4	8.0		2.1	+ 1.2	3.5		
		12 00 noon	482	1.001	22.1	18.0	9.8			— 2.7	1.0		
		2 00 p m	122	1.011	21.9	16.0	5.3		2.4	+ 1.6	2.3		
		4 30 p m	430	1.005	7.9	5.6	5.7		3.1	+ 2.1	3.1		
		6 30 p m	70	1.018	1.7	1.2	3.1		2.8	+ 1.9	3.1		
		9 00 p m	230	1.008	3.2	2.8	5.4		4.3	+ 2.5	5.3		
		7 00 a m	350	1.011	7.0	3.1	15.7		13.8	+ 7.4	10.9		
	Total		1,772	1.008	71.7	51.1	53.3			+ 14.0	29.2		
4/ 8	Total		1,711	1.008	49.9	39.6	52.8		26.5	+ 5.2	28.6		
4/ 9	Total		1,821	1.009	67.7	73.3	46.4		27.1	+ 0.3	29.6		

5/16	9 30 a m	70	1 019	63	48	51			35
	12 00 noon	380	1 003	148	106	100			20
	2 00 p m	70	1 020	86	65	44	38		33
	4 30 p m	155	1 012	95	39	81			45
	6 30 p m	145	1 011	39	44	31			44
	9 00 p m	445	1 013	56	66	30			30
	7 00 a m	360	1 015	206	239	158			152
	Total	1,625	1 013	693	627	497			359
5/17	9 30 a m	119	1 017	118	80	90			44
	12 00 noon	230	1 005	102	73	64			18
	2 00 p m	75	1 016	78	67	45	25		31
	4 30 p m	345	1 005	104	77	82			45
	6 30 p m	215	1 007	61	69	58			49
	9 00 p m	512	1 004	111	142	75			36
	7 00 a m	318	1 012	195	222	90			122
	Total	1,881	1 009	772	728	504			368
5/18	9 30 a m	80	1 013	87	67	60			37
	12 00 noon	395	1 004	258	246	86			14
	2 00 p m	110	1 011	100	102	27	28		31
	4 30 p m	410	1 006	122	146	60			38
	6 30 p m	85	1 018	47	46	51			33
	9 00 p m	416	1 006	82	74	77			33
	7 00 a m	304	1 016	106	75	195			128
	Total	1,800	1 009	802	756	556			310
5/19	Merbaphen, 2 cc intravenously at 9 30 a m								
	9 30 a m	65	1 021	53	40	61			40
	12 00 noon	382	1 004	226	183	78			14
	2 00 p m	371	1 003	638	520	74			23
	4 30 p m	187	1 003	227	160	57	47		27
	6 30 p m	120	1 010	63	36	48			26
	9 00 p m	250	1 003	35	34	60			28
	7 00 a m	505	1 009	75	69	162			53
	Total	1,880	1 003	1317	1042	740			174
5/20	Total	1,627	1 007	303	340	371			357
5/21	Total	1,779	1 008	551	682	387			351
5/22	Total	1,500	1 009	629	589	415			308
									299

* The valence was assumed to be 18
† Water scheduled for 7 30 p m was taken at 9 00 p m

TABLE 4—Effect of Diuretics on the Urinary Excretion of S A—Continued

Date, 1931	Medication	Time of Voiding	Volume, Cc	Specific Gravity	Chloride, M Eq	Sodium, M Eq	Potas sum, M Eq	Calcium, M Eq	Ammonia Nitrogen, M Eq	Titratable Acidity Minus Carbon Dioxide, M Lq	Inorganic Phos- phorus,* M Eq	Inorganic Sulphate M Eq	Total Nitrogen, Gm
5/23		9 30 a m	114	1.018	133	108	70				31		
		12 00 noon	515	1.007	183	145	118				13		
		2 00 p m	124	1.015	121	104	53				39		
		4 30 p m	420	1.005	117	110	86				40		
		6 30 p m	92	1.016	53	47	53				37		
		9 00 p m	520	1.005	54	74	58				43		
		7 00 a m	260	1.017	101	71	170				121		
		Total	2,045	1.008	762	659	608		413	+186	324		99
5/24		9 30 a m	205	1.007	110	74	94				38		
		12 00 noon	300	1.004	154	121	94				20		
		2 00 p m	130	1.015	128	130	39				33		
		4 30 p m	425	1.005	142	135	69				20		
		6 30 p m	135	1.008	62	63	41				34		
		9 00 p m	440	1.005	101	164	45				39		
		7 00 a m	335	1.013	164	182	140				116		
		Total	1,920	1.008	861	869	522				300		82
5/25		9 30 a m	65	1.017	69	17	52		31	+24	33		
		12 00 noon	385	1.003	188	137	109		28	+73	23		
		2 00 p m	90	1.015	94	83	37		27	+19	36		
		4 30 p m	330	1.003	99	91	55		26	+12	25		
		6 30 p m	97	1.010	45	38	46		33	+24	36		
		9 00 p m	462	1.003	77	91	57		31	+47	33		
		7 00 a m	235	1.015	118	106	134		137	+79	108		
		Total	1,664	1.008	690	596	490		311	+251	294		80
5/26	Metaphyllin, 2 cc intramuscularly at 9 30 a m	9 30 a m	59	1.026	57	41	53		25	+23	33		
		12 00 noon	321	1.012	404	383	127		25	+67	27		
		2 00 p m	183	1.011	182	181	53		24	+06	38		
		4 30 p m	37	1.008	123	123	83		26	+02	39		
		6 30 p m	79	1.016	42	35	45		33	+30	46		
		9 00 p m	419	1.006	17	82	46		36	+15	55		
		7 00 a m	310	1.015	58	59	148		149	+93	150		
		Total	1,728	1.010	913	907	555		319	+98	388		87
5/27		Total	1,720	1.008	432	351	463		320	+237	306		91
5/28		Total	1,147	1.010	533	377	618		357	+218	314		83

TABLE 4—Effect of Diuretics on the Urinary Excretion of S A—Concluded

Date, 1931	Medication	Time of Voiding	Volume, Cc	Specific Gravity	Chloride, M Eq	Sodium, M Eq	Potas- sium, M Eq	Calcium, M Eq	Ammonia Nitrogen, M Eq	Titratable Acidity Minus Carbon Dioxide, M Eq	Inorganic Phosphate Phos- phorus,* M Eq	Inorganic Sulphate M Eq	Total Nitrogen, Gm
6/ 7		9 30 a m	132	1.016	16.3	11.7	10.3				3.3		
		12 00 noon	354	1.005	15.1	11.4	8.5				1.4		
		2 00 p m	157	1.006	14.3	12.2	4.9				3.4		
		4 30 p m	391	1.005	9.5	6.3	8.3				3.5		
		6 30 p m	110	1.010	4.3	3.8	4.6				3.8		
		9 00 p m	410	1.003	4.5	6.1	7.2				3.0		
		7 00 a m	540	1.009	13.7	12.2	14.8				12.0		
		Total	1,894	1.007	77.7	63.7	56.6		30.9	+18.0	30.4		8.9
6/ 8		9 30 a m	84	1.019	8.3	6.4	6.6				3.8	3.7	
		12 00 noon	198	1.011	13.6	7.3	11.3				3.5	3.5	
		2 00 p m	107	1.013	5.8	3.9	5.3				4.5	2.3	
		4 30 p m	348	1.005	7.2	4.9	7.3				4.1	3.7	
		6 30 p m	349	1.005	5.7	6.0	4.8				4.1	3.5	
		9 00 p m	481	1.005	9.8	16.2	5.3				5.3	5.0	
		7 00 a m	351	1.013	16.0	13.5	14.1				14.6	14.8	
		Total	1,911	1.009	66.4	63.2	74.7		30.2		39.9	36.5	9.3
6/ 9		9 30 a m	150	1.012	15.0	7.6	7.0				3.5	3.2	
		12 00 noon	460	1.006	22.8	20.3	12.4				1.9	2.9	
		2 00 p m	137	1.011	10.8	9.6	3.9				3.4	2.5	
		4 30 p m	528	1.006	18.2	16.8	8.6				3.4	3.0	
		6 30 p m	250	1.005	7.8	9.1	3.2				3.3	3.5	
		9 00 p m	360	1.004	6.3	9.9	5.8				4.4	4.4	
		7 00 a m	380	1.011	14.6	15.9	15.3				16.0	12.8	
		Total	2,265	1.007	95.5	89.4	56.2		30.9		36.4	32.0	9.2
6/10	Salycrgan, 2 cc intravenously at 9 30 a m	9 30 a m	91	1.016	8.8	7.2	5.4	1.0			4.7	3.2	
		12 00 noon	361	1.008	34.2	30.6	7.6	1.6			1.6	2.4	
		2 00 p m	261	1.010	42.3	32.8	7.1	1.8			1.7	2.4	
		4 30 p m	370	1.006	11.8	10.1	7.0	0.6			3.3	2.8	
		6 30 p m	180	1.003	3.0	3.9	4.5	0.4			3.3	3.3	
		9 00 p m	490	1.006	6.9	11.7	6.9	0.8			4.6	4.3	
		7 00 a m	337	1.010	8.3	8.0	15.4	0.7			12.8	15.0	
		Total	2,090	1.008	115.3	104.3	53.9	6.9			32.0	33.1	9.5
6/11		Total	1,899	1.008	53.4	56.0	15.3		31.8		35.7	34.5	9.4
6/12		Total	1,823	1.008	60.8	56.9	50.7		29.7		37.6		
6/13		Total	1,955	1.009	58.6		58.3		30.8	+13.7	35.6		9.1
6/14		Total	2,728	1.007	98.7		63.2		31.2	+11.3	39.2		9.6

* The valence was assumed to be 18

potassium was not significantly altered. The relation between the excretion of sodium and that of chloride in this subject was qualitatively the same as that following merbaphen in S D. As observed following the other diuretics, the predominant excretion of the base sodium indicates that the diuresis following salyrgan represents fluid drawn mainly from the interstitial spaces.

Effect of 2 cc of Metaphyllin Intramuscularly on S A—The diuresis following the intramuscular injection of 2 cc of metaphyllin (table 4) appeared as promptly as it did in the other subjects after intravenous administration and persisted for four and a half hours after the injection (fig 6). In this patient the diuretic effect was significantly less

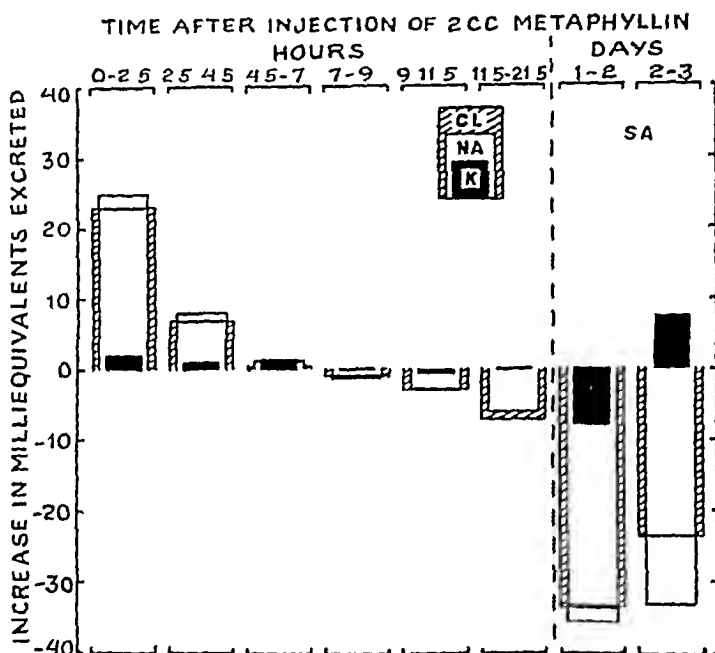


Fig 6—Net effect of the intramuscular administration of 2 cc of metaphyllin on the urinary excretion and subsequent retention of chloride, sodium and potassium in S A.

than that caused by 2 cc of the mercurial diuretics, salyrgan and merbaphen. The relation between the various inorganic ions excreted was similar to that observed in S D following 2 cc of metaphyllin.

Effect of Two Doses of 2 cc of Metaphyllin Intravenously on E W—The intravenous injection of 2 cc of metaphyllin on two separate occasions caused an increase in the volume of urine during the first eleven and a half hours after administration in both instances (table 5). The relation between the increased amounts of inorganic ions excreted (figs 7 and 8) was approximately that observed in S D and S A following 2 cc of metaphyllin. During the diuresis on the first occasion, the following increases were noted: sodium, 53, chloride, 41, potassium, 5,

TABLE 5—Effect of Diuretics on the Urinary Excretion of E W

Date, 1931	Medication	Time of Voiding	Volume, Cc	Specific Gravity	Chloride, M Eq	Sodium, M Eq	Potas sum, M Eq	Calcium, M Eq	Ammonia Nitrogen, M Eq	Titratable Acidity Minus Carbon Dioxide, M Eq	Inorganic Phosphate phorus,* M Eq	Inorganic Sulphate Sulphur, M Eq	Total Nitrogen, Gm
10/17		9 30 a m	64	1.016	4.0	5.3	2.0	0.2			1.9		
		12 00 noon	71	1.017	3.9	5.9	2.0	0.3			2.5		
		2 00 p m	93	1.014	3.5	6.0	2.0	0.5			3.6		
		4 30 p m	200	1.010	6.0	10.4	2.8	0.3			4.1		
		9 00 p m	331	1.011	9.1	19.5	3.7	0.5			6.9		
10/18		7 00 a m	355	1.010	43.9	57.8	10.7	1.1			11.4		
		Total	1,614	1.011	70.4	104.9	23.2	2.9	13.1	+ 5.2	30.4	34.2	3.8
		9 30 a m	74	1.017	6.1	7.2	1.5	0.3			2.6		
		12 00 noon	133	1.014	6.7	10.5	2.1	0.4			3.3		
		2 00 p m	52	1.018	3.1	4.9	1.3	0.2			2.5		
10/19		4 30 p m	146	1.015	7.3	12.4	3.8	0.3			4.8		
		9 00 p m	370	1.011	9.8	20.0	4.1	0.4			6.9		
		7 00 a m	612	1.011	29.8	38.9	9.3	0.9			10.5		
		Total	1,357	1.012	62.8	93.9	23.1	2.5	14.0	+10.2	30.6	35.1	8.7
		9 30 a m	82	1.015	5.7	7.3	2.4	0.3			2.7		
10/20	Metaphyllin, 2 cc intravenously at 9 30 a m	12 00 noon	130	1.011	5.7	8.7	2.1	0.4			3.3		
		2 00 p m	116	1.011	3.8	6.7	1.6	0.3			3.5		
		4 30 p m	180	1.010	3.6	6.8	1.5	0.2			3.0		
		9 00 p m	390	1.009	9.3	19.2	4.0	0.6			7.8		
		7 00 a m	785	1.008	38.8	49.0	11.6	1.1	12.1	+10.1	11.7	33.7	8.9
10/21		Total	1,633	1.009	66.9	91.7	27.2	2.9			32.0		
		9 30 a m	102	1.017	8.2	10.0	3.9	0.4			3.1		
		12 00 noon	265	1.012	22.2	30.8	2.8	1.2			3.4		
		2 00 p m	142	1.015	12.4	17.4	2.9	0.5			3.7		
		4 30 p m	113	1.015	9.8	13.4	2.7	0.3			2.8		
10/22		9 00 p m	534	1.010	20.9	35.7	7.2	0.6			9.2		
		7 00 a m	600	1.009	27.8	34.6	8.5	0.6			8.4		
		Total	1,736	1.010	101.3	141.7	28.9	3.6	12.2	+ 2.2	30.6	34.2	9.2
		Total	1,352	1.011	51.2	74.7	21.9	2.4	14.1	+14.1	28.7	35.2	9.0
		Total	1,839	1.010	50.1	76.8	19.1	3.3	15.0	+11.5	31.4		9.2
10/23		Total	1,555	1.012	63.3	94.5	22.6	3.2	14.1	+ 7.1	31.7		9.2
		Total	1,663	1.011	69.5	100.5	24.0	3.3	15.6	+ 7.3	29.0		9.2

and calcium, 1.2 milliequivalents. On the second occasion the increases were sodium, 64, chloride, 50, potassium, 63, and calcium, 1.4 milliequivalents. These amounts are less than those observed in S. D. following the intravenous administration of 2 cc of metaphyllin. However, the variations on control days were slight (table 5), and the relative response in the four individual periods of diuresis on each occasion was so constant (figs 7 and 8) that calculations concerning the loss of body fluid are significant. With the considerations outlined, the calculated loss of body fluid represented by the increases in urinary sodium and potassium during the diuresis on the first occasion was approximately 370 cc for extracellular and 20 cc for intracellular fluid, making a total of 390 cc. The chloride content of this amount of body fluid is approximately 43 milliequivalents, which compares well with the actual excess excretion of 41 milliequivalents of urinary chloride. The calcium content of this amount of body fluid is approximately 1.5 milliequivalents and is significantly similar to the actual excess urinary excretion of 1.2 milliequivalents. The increase in urinary volume observed during the diuresis was 425 cc as compared to the calculated loss of 390 cc of body fluid. Likewise, on the second occasion, the amount calculated for the extracellular fluid was approximately 440 cc, and that for the intracellular fluid, 30 cc, making a total of 470 cc. The chloride content of this amount of body fluid is approximately 52 milliequivalents, which compares well with the observed increased excretion of 50 milliequivalents of urinary chloride. The calcium content could be expected to be 1.9 milliequivalents, which is comparable to the observed excretion of 1.4 milliequivalents. The increase in urinary volume observed during the diuresis on this occasion was 580 cc as compared with the calculated loss of 470 cc of body fluid. The degree of correspondence of all these calculated and observed values is surprisingly close when one considers the pitfalls which may be encountered in the study of water and salt metabolism. After the diureses caused by metaphyllin in E. W., as in all other instances, there followed a compensating retention of water and salts (table 5).

Urinary Output of Inorganic Phosphate, Inorganic Sulphate, Total Nitrogen, Ammonia and Titratable Acid and Specific Gravity of the Urine During Diuresis—No significant changes in the urinary excretion of inorganic phosphate could be detected following the administration of any of the mercurial or xanthine diuretics studied. Keith and Whelan³⁴ likewise found no significant changes in the twenty-four hour urinary output of inorganic phosphate following the administration

³⁴ Keith, N. M., and Whelan, M. A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, *J. Clin. Investigation* 3: 149, 1926.

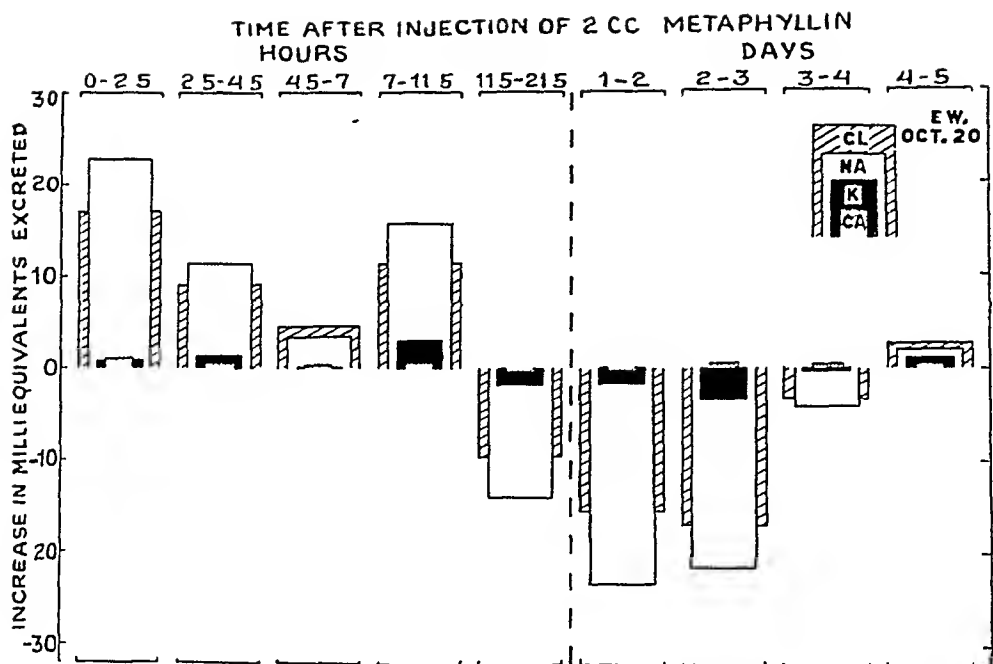


Fig 7—Net effect of the intravenous administration of 2 cc of metaphyllin on the urinary excretion and retention of chloride, sodium, potassium and calcium in E W

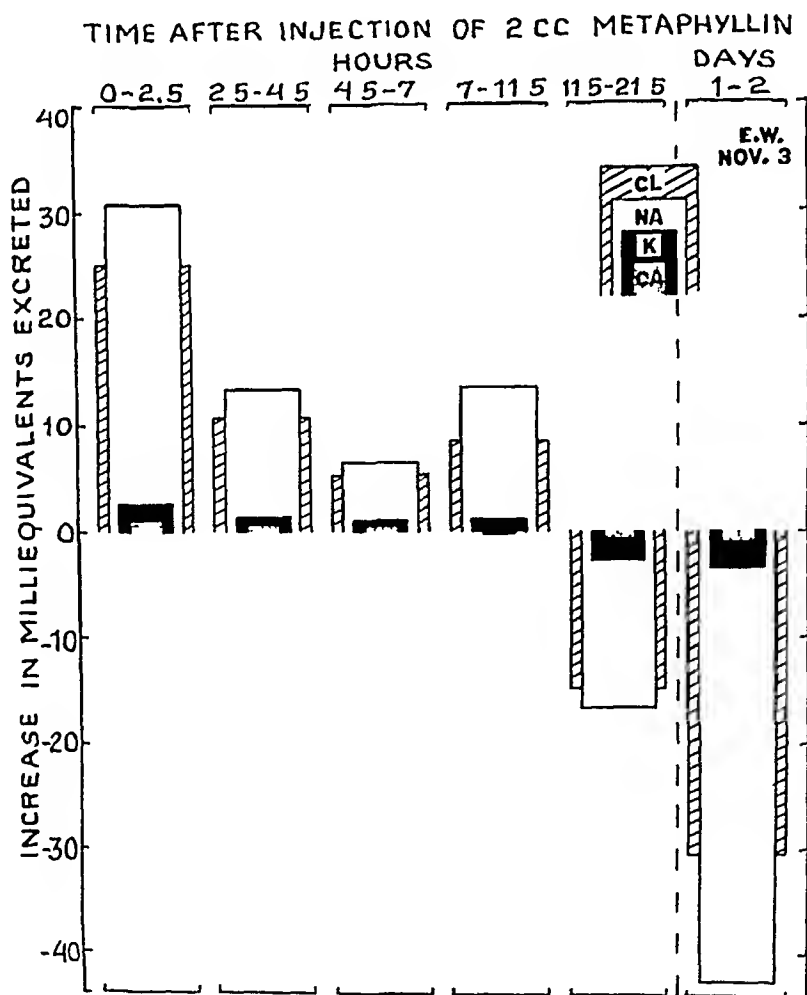


Fig 8—Net effect of the intravenous administration of 2 cc of metaphyllin on the urinary excretion and retention of chloride, sodium, potassium and calcium in E W Figure 8 is to be compared with figure 7 which also shows the effect of 2 cc of metaphyllin in this subject on another occasion

of 2 cc of merbaphen in normal men. Other investigators³⁵ have found a decrease in the excretion of inorganic phosphate during the diureses caused by metaphyllin and theobromine sodium salicylate, while an increased excretion has been observed during the diureses caused by sodium nitrate, sodium chloride, sodium sulphate and urea³⁶. The absence of appreciable changes in the excretion of inorganic phosphate during the diureses observed in our studies is consistent with the concept that the effect of the diuretics studied is mainly to cause a loss of body water with its constituent inorganic ions. The amount of inorganic phosphate in 1 liter of normal interstitial fluid is approximately from 2 to 3 milliequivalents. The largest diuresis observed in the aforementioned studies (S D following 2 cc of merbaphen) was approximately 1 liter. Even in this instance the added amount of urinary inorganic phosphate which one might expect to be excreted on this basis (from 2 to 3 milliequivalents) could not be detected accurately under the conditions of the study, since the output of inorganic phosphate in the control periods, corresponding to the nine-hour period of diuresis, varied by this amount. The important fact is, therefore, that beyond these limits no changes in the excretion of phosphate were observed following either the mercurial or the xanthine diuretics studied.

The excretion of inorganic sulphate was studied in divided periods following the administration of 2 cc of merbaphen, 2 cc of salyrgan and 2 cc of metaphyllin (tables 3, 4 and 5). The excretion of inorganic sulphate during diuresis did not differ appreciably in any instance from that in the control periods. This finding is consistent with the fact that inorganic sulphate is present in extremely small amounts in normal body fluids.

Measurements of the output of total nitrogen in the urine were made for periods of twenty-four hours throughout the studies. The output of total urinary nitrogen was not affected in any of the studies (tables 3, 4 and 5).

Studies of the urinary excretions of titratable acid (minus carbon dioxide) and of ammonia during the aforementioned diureses corroborated certain of the other findings. In all the studies following the administration of mercurial diuretics, with the exception of observations on S D following 2 cc of merbaphen, the additional excretions of fixed acid (chloride) and fixed base constituents (sodium, potassium and calcium) were so nearly the same that no change in titratable acidity or ammonia was anticipated, and none was found. In S D following 2 cc of merbaphen the excess chloride excreted during the diuresis

35 Bolliger, A. The Influence of the Purine Diuretics on Inorganic Phosphates of Blood and Urine, *J Biol Chem* **76** 797, 1928.

36 Hendrix, B. M., and Calvin, D. B. The Loss of Bases in Diuresis and Its Effect upon the Alkali Reserve of the Blood, *J Biol Chem* **65** 197, 1925.

exceeded the sum of the amounts of sodium, potassium and calcium³⁷ excreted by approximately 20 milliequivalents. The urinary excretion of ammonia was slightly increased, the titratable acidity remaining within the limits of the control variations (table 3).

In E W on the two occasions following metaphyllin, the ammonia and titratable acidities were measured for periods of twenty-four hours. The excretion of ammonia was not affected. The titratable acidity (minus carbon dioxide) decreased appreciably on both of the days of diuresis. This finding is in accord with the fact that the excess excretions of fixed base exceeded those of fixed acid in amounts closely approximating those for normal interstitial body fluids. (The bicarbonate or "volatile acid" of normal interstitial fluid is approximately 30 milliequivalents per liter²⁶.) In S D following 2 cc of metaphyllin the excretion of ammonia did not differ significantly from that on control days, the titratable acidity was not measured. In S A the excretion of ammonia following 2 cc of metaphyllin did not differ significantly from that on control days. The titratable acidity tended to be lower than on most of the control days, although on control days the variation of titratable acidity was such that interpretation must be guarded. The apparent lowering of the titratable acidity is in harmony with the observations on E W following 2 cc of metaphyllin.

According to the concept that the increased urinary excretion following the diuretics studied represents definite volumes of body fluids, the specific gravity of the excess fluid excreted during the diuresis would be approximately 1.009, a value representative of protein-free interstitial fluid. In each period of diuresis the increased amount of urine excreted constituted but a part of the entire specimen of urine, the specific gravity of which was measured. Consequently one would expect the specific gravity of each specimen (during the periods of diuresis) to be closer to 1.009 than during analogous control periods. The variations in the specific gravity of the urine during the control periods were relatively great, so that an exact evaluation of the specific gravities of the additional fluids excreted during the diuresis is not possible in these studies. In cases with pathologic conditions with edema, to be reported later, in which the specific gravities of the urine were more constant on control days and the volume of diureses greater than those observed in this study, the specific gravity of the excess fluid excreted during the diuresis, as calculated from the specific gravities and volumes for control periods and periods of diuresis, was demonstrated to be close to 1.009.

³⁷ The excretion of magnesium was not determined in any of the experiments but probably the increase amounted to not more than 3 milliequivalents during any diuresis.

Effect of Diuretics on the Excretion of Water and Salt in the Stools
—Since appreciable amounts of water and inorganic salts are normally excreted in the stools, it seemed necessary, in a complete study of the effects of the diuretics on the water and salt metabolism, to learn to what extent the fecal excretion of these substances was affected by the drugs. The stools collected during certain periods when no medication was given were analyzed for their content of water, sodium, chloride, potassium, phosphorus and calcium, and the results were compared with those obtained when diuretics were being administered (table 6). The fecal excretion representing periods of diuresis is necessarily calculated from three day periods, although the drug was administered on only one of these days. This method is the most satisfactory one available and should reveal any important change in fecal excretion during the

TABLE 6—*Analyses of Stools*

Sub ject	Period	Date When Period Began	No of Days in Period	Medication*	Water, Gm per Day	Chlo ride, M Eq per Day	Sodium, M Eq per Day	Potas sium, M Eq per Day	Cal cium, M Eq per Day	Phos phorus, M Eq per Day
S D	1	3/22/31	4	None	81	3.7	0.4	5.9	12.5	10.4
	2	3/26/31	3	None	66	2.3	1.3	7.1	15.0	9.2
	3	3/29/31	3	None	68	3.1	2.6	6.4	14.0	10.9
	4	4/1/31	3	None	97	4.2	1.3	11.5	15.5	14.4
	5	5/22/31	3	Merbaphen, 2 cc	88	4.2	1.3	11.2	17.5	14.4
	6	6/9/31	3	Metaphyllin, 2 cc	104	3.4		8.4	19.5	16.7
S A	1	3/22/31	6	None	47	2.0	0.9	7.9		18.4
	2	3/28/31	4	None	99	3.1	2.6	11.5		26.4
	3	4/1/31	6	None	55	2.5	1.3	7.9		17.8
	4	4/7/31	3	Merbaphen, 2 cc	62	4.2	2.2	15.1		18.4
	5	5/19/31	3	Merbaphen, 2 cc	63	3.4	1.7	10.2		17.3
	6	5/26/31	3	Metaphyllin, 2 cc	98	4.5	1.3	10.2		23.0
	7	6/10/31	3	Salyrgan, 2 cc	60	3.4	0.4	10.2		29.8

* All the drugs were given on the first day of the period.

period of diuresis. If there were, for instance, an increase of more than approximately 0.1 Gm of sodium or 0.3 Gm of chloride during the diuresis, the retention during the remainder of the three day period in which the stools were examined could not possibly be entirely compensatory, even though no sodium or chloride was excreted during this time (table 6).

The amounts of water and inorganic constituents in the stools representing periods during which diuretics were given did not differ appreciably from the amounts of these substances present when no drugs were administered (table 6). No toxic gastro-intestinal effects were noted clinically except in S. A. during period 5 (table 6). He experienced moderate abdominal cramps during the first twelve hours after 2 cc of merbaphen, and on that day passed four small stools of normal consistency. These findings indicate that, under conditions similar to those of this study, in the absence of diarrhea it is unnecessary to include an examination of the stools in evaluating the effect of diuretics on the water and salt metabolism.

Effect of Diuretics on the Insensible Loss of Water—As shown by Wiley and his co-workers,³⁸ studies of water metabolism involve four sources of intake, namely, the water drunk, water in food, water of oxidation and preformed water, and three sources of elimination, namely, urine, stools and insensible perspiration. The common clinical method of using the water drunk and the urinary water excreted as an index of change in water balance in the body is valid only for comparative changes when all the other stated factors remain relatively constant.

To determine whether in normal persons the increase of water in the urine following the administration of diuretics under the conditions of our experiments is an accurate measure of the increased loss of water from the body, it is necessary first to determine to what extent the diuretics cause changes in the other paths of elimination, namely, the stools and the insensible perspiration. It has been shown that the various diuretics caused no appreciable changes in the amount of water secreted in the stools. This factor, therefore, need not be taken into account in evaluating comparative losses of water from the body in control periods and in periods of diuresis.

The insensible loss of weight has been studied in S D and S A (table 7) during control periods and during similar periods following the administration of diuretics. For purposes of comparison, calculations have been made for the periods including the four and a half hours from 9 30 a m to 2 p m, the routine schedule (table 1) including dinner at 12 noon being adhered to as usual. In each instance the subjects remained in bed in a sitting or lying posture. The room temperature was not above 78 F, the humidity relatively constant, and the activity of the subjects controlled for the experimental periods. The diuretic was administered in each case at 9 30 a m, and the greatest diuresis always occurred between that time and 2 p m. Consequently whatever changes occurred in insensible loss of water coincident with an increase in urinary output during the diuresis would be apparent in this period.

The following considerations are necessary for the interpretation of the data. The total insensible loss is calculated from the following formula: insensible loss of weight = weight at 9 30 a m — (weight at 2 p m — ingesta + urine + stool + blood drawn). The insensible loss of weight is the resultant of the weight of the insensible water lost, the weight of the carbon dioxide exhaled and the weight of the oxygen absorbed.^{38b} Expressed as an equation in which the weight of each substance is employed: insensible loss of weight = $H_2O + (CO_2 - O_2)$

38 (a) Wiley, F H, and Newburgh, L H. The Relationship Between the Environment and the Basal Insensible Loss of Weight, *J Clin Investigation* **10** 689, 1931. (b) Newburgh, L H, Wiley, F H, and Lashmet, F H. A Method for the Determination of Heat Production Over Long Periods of Time, *ibid* **10** 703, 1931.

The ($\text{CO}_2\text{—O}_2$) factor is a function of the metabolic mixture utilized by the patient and amounts to a small portion of the total loss, which portion may be considered constant under the conditions of our studies. The changes in total insensible loss of weight therefore represent a measure of the changes in the insensible loss due to water. In S D the insensible loss was determined for three control periods from 9 30 a m to 2 p m and gave an average of 89 Gm per hour. Similarly, determinations made after the administration of 2 cc of merbaphen, 3 Gm of theobromine sodium salicylate and 2 cc of metaphyllin averaged

TABLE 7—*Insensible Loss of Water During the First Four and a Half Hours Following Diuretics Compared to Similar Periods When no Diuretics Were Administered*

Subject	Date	Medication	Insensible Loss of Weight (9 30 a m to 2 00 p m) Gm per Hour
S D	5/21/31	None	114
	5/22/31	Merbaphen, 2 cc	93
	5/23/31	None	66
	6/ 9/31	Metaphyllin, 2 cc	80
	6/10/31	None	75
	6/29/31	None	74
	6/30/31	None	79
	7/ 1/31	Theobromine sodium salicylate, 3 Gm	63
S A	4/ 3/31	None	39
	4/ 6/31	None	50
	4/ 7/31	Merbaphen, 1 cc	46
	4/ 8/31	None	38
	5/18/31	None	38
	5/19/31	Merbaphen, 2 cc	43
	5/20/31	None	51
	5/25/31	None	42
	5/26/31	Metaphyllin, 2 cc	49
	5/27/31	None	71
	6/ 2/31	None	72
	6/ 3/31	Salyrgan, 1 cc	35
	6/ 9/31	None	33
	6/10/31	Salyrgan, 2 cc	37
	6/11/31	None	32

79 Gm per hour. Comparative figures for periods during which there was a retention of sodium, chloride and water following the diureses caused by merbaphen and metaphyllin averaged 71 Gm per hour.

In S A the insensible loss was determined on six control days and averaged 39 Gm per hour. The results of similar determinations made following the administration of 1 and 2 cc of merbaphen, 1 and 2 cc of salyrgan and 2 cc of metaphyllin averaged 42 Gm per hour. The results of determinations made on four different days during the periods of retention following diuresis gave an average insensible loss of 52 Gm per hour.

The variability in the total insensible loss for the four and a half hour periods studied was considerable on control days. This same

observation was made by Wiley and Newburgh³⁸¹ who cited the difficulties of determining complete water balances over short periods of time. The fluctuations in the volume of urine during the aforementioned individual periods of control days were not significantly dependent on these relatively minor fluctuations in insensible loss of water.

The various diuretics produced no significant effect on the insensible loss of water during the periods of diuresis or retention. The variability in the amount of the insensible loss of water during the periods of diuresis and retention was similar to that of the control periods.

TABLE 8—*Effect of Diuretics on the Serum of Normal Persons*

Subject	Medication	Date	Hour	Chloride, M Eq per Liter	Sodium, M Eq per Liter	Specific Gravity
S D	Metaphyllin, 2 cc at 9 30 a m	6/ 9/31	9 25 a m	101	142	1 0272
			11 10 a m	99	142	1 0274
			12 25 p m	98	138	1 0274
			1 40 p m	99	138	1 0276
S A	None	4/ 6/31	9 25 a m	98		
			10 05 a m	99		
			12 00 noon	100		
			2 00 p m	98		
	Merbaphen, 1 cc at 9 30 a m	4/ 7/31	9 25 a m	99		
			10 05 a m	99		
			12 00 noon	99		
			2 00 p m	98		
	Salyrgan, 1 cc at 9 30 a m	6/ 3/31	9 25 a m	99	142	1 0271
			11 25 a m	100	142	1 0265
			12 25 p m	101	142	1 0262
			1 40 p m	100	142	1 0265
	None	6/ 4/31	9 40 a m	100		1 0271
			9 25 a m	100	145	1 0269
			11 25 a m	100	144	1 0263
			12 25 p m	99	145	1 0264
			1 40 p m	100	145	1 0265
E W	None	11/2/31	9 25 a m	97	137	1 0256
			12 00 noon	96	136	1 0243
	Metaphyllin, 2 cc at 9 30 a m	11/3/31	9 25 a m	96	137	1 0257
			12 00 noon	97	137	1 0259

These findings lead to the conclusion that the effect of diuretics in normal persons can be evaluated without introducing calculations of the insensible loss of water, provided the conditions of room temperature, humidity and activity of the subject are controlled as they were in these studies.

Effect of Diuretics on Serum Constituents—The results of repeated analyses of the blood serum for sodium chloride and specific gravity at intervals before, during the height of and after the diuresis did not differ appreciably from those obtained at similar times on control days (table 8). Since the urinary analyses showed that the increased excretions during these periods of diureses, in which hematologic studies were made (table 8), were of the approximate composition of body fluids, one would not expect a measurable change in the concentrations of the serum

electrolytes studied in these instances Keith and Whelan³⁴ analyzed the blood of normal subjects for various constituents before, and approximately six and twenty-four hours after, the administration of merbaphen. No constant changes were observed, but in the absence of measurements of the urine during the first few hours after the administration of the drug the significance of their results is not clear. In S. D., calculations of the nature of the fluid excreted during the diuresis following 2 cc. of merbaphen showed the excretion of chloride to be somewhat in excess of that expected on the basis of the chloride composition of a volume of body fluid equal to the volume excreted during the diuresis. Analyses of serum were not made in this instance. Since the total amount of urine excreted during the period of diuresis was approximately 1 liter, it seems possible that a slight measurable lowering of the serum chloride concentration might have been detected. In a series of cases of pathologic edema, to be reported later, in which salyrgan and merbaphen caused diureses of from 1 to 5 liters, analyses of the serum chloride usually showed appreciable decreases (amounting to as much as 10 milliequivalents in one instance), and the serum bicarbonate showed closely compensatory increases. The serum base was unchanged. The reported hematologic observations following diuretics in pathologic conditions have been adequately reviewed by Schmitz³⁹.

Effect of Diuretics on the Rate of Glomerular Filtration and Tubular Reabsorption—According to the current concept of renal function the increased excretion of water and certain inorganic ions following diuretics may be accomplished by an increase in glomerular filtration or by a decrease in tubular reabsorption, these changes being either absolute or relative. To estimate the relative importance of these two factors during the diuresis we have measured the rate of glomerular filtration and of tubular reabsorption according to the method of Rehberg,²² slightly modified (table 9). The validity of the Rehberg test as a measure of the rate of glomerular filtration is not universally accepted. Even though the method may contain absolute errors, relative changes before and during the diuresis may still provide insight into the action of the diuretics. The technic used differed from that described by Rehberg in that no creatinine was fed and the Fohn method of measurement of creatinine²³ was employed. It seemed inadvisable to feed creatinine in these studies since its effect on water and salt metabolism is not established. The modified method employed was satisfactory for our purposes. Check analyses of the same samples of blood serum and of urine showed good agreement. The values for serum creatinine varied somewhat from day to day in the

39 Schmitz, H. L. The Effect of Euphyllin and Salyrgan upon Glomerular Filtration and Tubular Reabsorption, *J. Clin. Investigation* **11** 1075, 1932.

TABLE 9—*Effect of Diuretics on the Rate of Glomerular Filtration and on Tubular Reabsorption.**

Subject	Date	Medication	9 30 a m to 12 Noon					12 Noon to 2 p m				
			Rate of Glomerular Filtration, Cc per Minute		Urea Clearance, per Cent of Normal			Rate of Glomerular Filtration, Cc per Minute		Urea Clearance, per Cent of Normal		
			Volume of Urine, Cc per Minute	Output of Chloride, Gm	Reabsorbed Fluid, per Cent of Filtered	Urea Clearance, per Cent of Normal	Volume of Urine, Cc per Minute	Output of Chloride, Gm	Reabsorbed Fluid, per Cent of Filtered	Urea Clearance, per Cent of Normal	Volume of Urine, Cc per Minute	Output of Chloride, Gm
S D	5/21/31	None	106		99.2		0.94	0.97	97		1.19	0.53
	5/22/31	Merbaphen, 2 cc	119		97.4		3.06	2.64	85		4.02	3.52
	6/ 9/31	Metaphyllin, 2 cc	91		95.6	95 (M)	4.02	2.16	95	136 (M)	3.20	1.54
	7/ 1/31	Theobromine sodium salicylate, 3 Gm	80		96.6	110 (M)	2.68	1.25	80	138 (S)	1.12	0.53
S A	5/18/31	None	65		96.0		2.63	0.92	53		0.92	0.46
	5/19/31	Merbaphen, 2 cc	60		95.8		2.54	0.80	61		3.10	2.27
	5/25/31	None	67		96.2		2.57	0.67	68		0.75	0.34
	5/26/31	Metaphyllin, 2 cc	75		97.0		2.21	1.43	66		1.52	0.65
	6/ 3/31	Salysrgan, 1 cc	69		95.8		2.88	1.13	70		1.52	0.53
E W	11/2/31	None	52		98.1		1.02	0.21	55		1.04	0.20
	11/3/31	Metaphyllin, 2 cc	57		94.1		3.40	1.04	59		2.06	0.56
J S	10/6/32	None	73		90.4	99 (S)	0.39	0.22				
	10/7/32	Metaphyllin, 2 cc	75		93.9	86 (M)	4.65	7.28				
B E	10/7/32	None	50		97.4	77 (S)	1.35	0.55				
	10/5/32	Metaphyllin, 2 cc	67		94.4	92 (M)	3.79	2.12				

* All the drugs were given at 9 30 a m (M) refers to maximum and (S) to standard urea clearances

same subject, but repeated analyses at different times on a given day during the periods studied showed that the value for serum creatinine was constant. The values found probably include other chromogenic substances besides creatinine, but for the comparative purposes of this study such a limitation does not seem important. These considerations are corroborated by studies in two additional subjects in whom the amount of creatinine in the blood was increased by creatinine feeding to approximately 6 mg per hundred cubic centimeters. In these instances the results before and during the diuresis lead to the same interpretation of the effects of the diuretics as in the instances in which creatinine was not fed.

The rate of glomerular filtration as measured by the creatinine clearance was not altered significantly during periods of marked diuresis following either the xanthine or the mercurial diuretics (table 9). The volume of urine excreted per minute and the excretion of chloride during the diuresis were at times several hundred per cent greater than during control periods and bore no relation to changes in the rate of glomerular filtration. In S. D., for instance, the rate of glomerular filtration on the day when no medication was given was 106 cc per minute during the period from 9:30 a. m. to 12 noon, and the volume of urine was 0.9 cc per minute. During similar periods following 2 cc of metaphyllin and 3 Gm. of theobromine sodium salicylate the rates of glomerular filtration were 91 and 80 cc per minute and the volumes of urine, 4 and 2.7 cc per minute, respectively (table 9).

These results indicate that the diuresis observed in our subjects cannot be attributed to changes in the rate of glomerular filtration. Values for urea clearance following diuretic drugs were also obtained in certain instances (table 9), and the findings are in agreement with this concept.

The amount of tubular reabsorption has been calculated by subtracting the volume of urine in cubic centimeters per minute from the rate of glomerular filtration in cubic centimeters per minute. To reduce our results to a comparable basis, the tubular reabsorption has been expressed in percentage of the rate of glomerular filtration for each period. A decrease in the percentage of tubular reabsorption was observed in every instance during the diuresis. Similar calculations on the basis of the amounts of sodium and chloride present in the serum and urine show that the tubular reabsorption of sodium and chloride is likewise reduced following the administration of these diuretics. These observations indicate that in normal subjects the increased excretion of water and salts by the kidneys, following the diuretics studied, is accomplished by a relative decrease in the tubular reabsorption of these substances. Likewise Schmitz,³⁹ in experiments on dogs, and

Herrmann and his co-workers,⁴⁰ in studies on patients with cardiac edema, have shown that the mercurial diuretics cause a decrease in the percentage of tubular reabsorption with no significant effect on the rate of glomerular filtration. These authors, however, found significant increases in the rate of glomerular filtration following metaphyllin. The conditions under which these results were obtained differed in important respects from those employed in our studies. Since Schmitz gave to dogs the same amount of metaphyllin as we administered to our subjects, the dosage in his experiments was proportionately many times greater. The dosage of metaphyllin employed by Herrmann was also larger than the usual clinical dose used by us, and his studies were made on patients with cardiovascular disease. Under these conditions this drug may act in a different manner. Our results, which indicate that in normal persons the diureses following both the mercurial and the xanthine diuretics cannot be attributed to increases in rates of glomerular filtration, are in harmony with those obtained in normal subjects by Chrometzka and his co-workers⁴¹ and by Gavazzeni,⁴² who used the usual Rehberg method with the feeding of creatinine.

COMMENT

There are certain points in common to all the aforementioned studies of the water and salt metabolism in normal subjects following the administration of both the xanthine and the mercurial diuretics. 1 The output of water, sodium, chloride, potassium and calcium is increased after the diuretics (fig 9). 2 The increases in water and in the bases—sodium, potassium and calcium—bear a constant relation to each other, the data indicate that the fluid lost from the body during diuresis was derived mainly from the interstitial body compartment. 3 There is no significant change in the phosphate, sulphate, ammonia or total nitrogen metabolism. 4 The increases in the excretion of water and fixed base in the urine following the various diuretics represent the loss of equivalent volumes of body fluids with their basic constituents. 5 The water and salts lost from the body of these subjects with normal water balances during the diuresis are regained by a compensatory retention. 6 There is no significant change in the insensible loss of water or in the water or salt content of the stools.

40 Herrmann, G., Stone, C. T., and Schwab, E. H. Some Studies on the Mechanism of Diuresis in Patients with Congestive Heart Failure, *Tr. A. Am. Physicians* **47** 279, 1932.

41 Chrometzka, F., and Unger, K. Untersuchungen über die Grösse des Glomerulusfiltrats unter dem Einfluss von Diuretika und Hormonen, *Ztschr. f. d. ges. exper. Med.* **80** 261, 1931.

42 Gavazzeni, M. Filtrato glomerulare e diuretici, *Policlinico (sez. med.)* **39** 236, 1932.

7 In the instances reported no significant changes were observed when repeated analyses of the blood serum for sodium, chloride and specific gravity were made at intervals before, during the height of, and after, the diuresis. 8 Measurements of the rate of glomerular filtration and tubular reabsorption according to the method of Rehberg, somewhat modified, indicate that the increased excretion of water and salts is accomplished by a relative decrease in tubular reabsorption, the rate of glomerular filtration remaining unaffected.

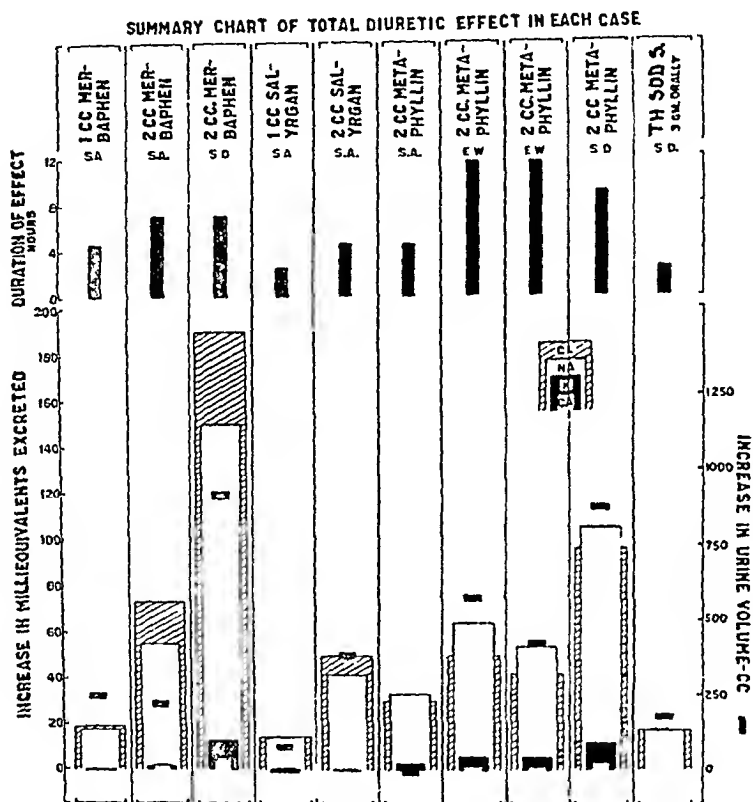


Fig 9—Summary of the net effect of the diuretic drugs on the duration of diuresis and on the excretion of water, chloride, sodium, potassium and calcium

The output of chloride following the xanthine diuretics compared well with that expected from the loss of body fluid as calculated on the basis of the losses of water and fixed base. Following the mercurial diuretics, the excretion of chloride was somewhat greater than that expected. Corresponding with these findings the titratable acidity was decreased following the xanthine and unchanged following the mercurial diuretics.

These considerations show that in general the effect of the different diuretics studied is qualitatively the same, the essential difference being in the magnitude and duration of the effect. A general comparison of the magnitude and duration of the effect of the various diuretics in our

subjects (fig 9) reveals reasons for the many discrepancies between the results reported in the literature. Previous studies have been concerned mainly with a comparison of the effect of diuretics in different patients who have shown considerable variation in their clinical state, or they have been confined to the effect of one type of diuretic on the twenty-four hour specimens of urine of normal persons. Under the standard conditions employed in the present investigation, examination of the numerous specimens of urine has shown that the mercurial and xanthine diuretics have a general relation to each other in regard to their potency in the same subject. The mercurial diuretics, merbaphen and salyrgan, were more effective than the xanthine diuretics, metaphyllin and theobromine sodium salicylate, when the usual clinical dose was administered. This relation was present consistently in each subject (fig 9). The period of maximum diuresis generally occurred during the first two and a half hours following the xanthine, and between two and a half and four and a half hours following the mercurial diuretics. The general level of response to all the diuretics was greater in one subject than in another. S D showed a greater response to merbaphen than S A, and a greater response to metaphyllin than either S A or E W. This variation in response to the same diuretic in different subjects emphasizes the value of comparative studies in the same person. The difference in response shown by various subjects may be related to body size. The largest response to a given diuretic was always observed in the largest subject (S D), in whom the total amount of body fluids available for excretion was presumably the greatest. Although the size of the kidneys may also be an important factor, the same relation between the magnitude of the diuresis and the amount of body fluid available for excretion has also been observed by us in pathologic conditions with edema, i e., in a patient with edema the diuretic effect of a drug decreases as the patient becomes less edematous. Further, the work of Lie⁴³ indicates that in a normal subject the diuretic response to caffeine is increased when isotonic salt solution is administered previous to the diuretic. The duration of the effect of the diuretics, likewise, showed considerable variability from person to person, although, in general, the magnitude and duration of effect were directly related to one another.

In comparing the effects of the diuretics there is an underlying assumption that under strictly comparable conditions in the same person a given amount of a drug produces a closely similar effect on different occasions. To test the validity of this assumption, the same amount of metaphyllin was given to E W on two separate occasions when his condition by all available tests seemed the same. Both times the responses were in satisfactory agreement in regard to the relation between the

43 Lie, E. Caffein and Diuresis in Man, *Am J Physiol* **92** 619 1930

various constituents and the absolute amounts excreted. Similarly, when different doses of the same diuretic were given to the same subject there was a definite relation between the amount of the dose and the magnitude and duration of the response. Doubling the dose approximately doubled the duration of the effect and trebled the magnitude of the diuresis.

Throughout this investigation repeated examinations of the urine were made for albumin, casts and cellular elements. No evidences of possible irritative renal effects were observed. Except for vomiting after 4 Gm of theobromine sodium salicylate by mouth in the same subject and for abdominal cramps, but no watery diarrhea, after 2 cc of merbaphen, no toxic effects were noted after any of the diuretics.

As shown previously in this communication, the proportions of the individual bases in the extra amounts of fixed base excreted during the diuresis were the same as those in the body fluids, and these bases were excreted with an extra volume of water which, in general, conformed to the expected amount of body fluid.

These considerations indicate that the diuretics cause an excretion of definite volumes of body fluids. The increase in the fixed bases excreted in the urine during diuresis is the base content of the body water lost. This finding reflects the obstinacy with which the organism maintains the constancy of the total electrolyte concentration of its internal environment and is a further illustration of homeostasis.⁴⁴ These results of the action of diuretics are analogous to the observations of Gamble and his co-workers²⁴ in studies of the metabolism of a fasting subject and furnish strong support for his interpretation of the urinary excretion in his subject in terms of body fluids. The calculations of the relative percentages of intracellular and extracellular water excreted indicate that the source of the body water excreted was almost entirely extracellular, the intracellular amounts being only 10 per cent or less of the total. While such calculations are inevitably only approximations, they are in accord with the concept of the importance of the lability of the extracellular body fluids in maintaining the constancy of the volume of intracellular fluids. This is suggested not only by the smaller amounts of intracellular fluid excreted, as indicated by the excretion of potassium (fig 9), but also by the fact that the excretion of intracellular fluid tended to be greater after the initial withdrawal of considerable amounts of extracellular fluids (figs 1 and 2). This action of the mercurial and xanthine diuretics in liberating more readily the extra-

⁴⁴ Cannon, W. B. *The Wisdom of the Body*, New York, W. W. Norton & Company, 1932.

cellular water in the body is similar to the action of the acid-producing salts in the patients studied by Gamble and his co-workers⁴⁵

The amounts of water and salts retained during the periods following diuresis consistently amounted to somewhat more than the amounts lost during that period (figs 1, 2 and 6). This slight overcompensation was followed by a secondary excess output immediately following, which resulted in the restoration of the original store of body water. This phenomenon of overcompensation is often encountered in the study of physiologic mechanisms. The compensatory retention of substances lost during diuresis in normal subjects is in marked contrast to the course of events following the dissipation of edema with diuretics in pathologic conditions.

To gain information regarding the mechanism of diuresis in our subjects, studies of the blood for sodium, chloride and specific gravity were repeatedly made at intervals before, during the height of, and after, the diuresis. The negative results of these studies are opposed to the opinions of investigators who believe that diuresis following diuretic drugs is initiated by the kidneys in response to measurable changes in the blood. Our results are in accord with the theory that a loss of the various inorganic ions and of water by the blood stream is immediately compensated by an influx from extravascular sources. The considerations discussed earlier in this communication indicate that the sources of this extravascular fluid are predominantly extracellular and to only a slight extent intracellular.

Experiments to elucidate the nature of the action of the various diuretics on the human kidney are difficult to design. Assuming the validity of the considerations underlying the determination of the rate of glomerular filtration by the method of Rehberg, our studies show that in normal subjects neither the mercurial nor the xanthine diuretics studied have an effect on the rate of glomerular filtration but cause an increase in the amount of urine and its constituents by a relative decrease in tubular reabsorption.

CONCLUSIONS AND SUMMARY

1 Eleven studies on three normal subjects were undertaken in order to define more accurately the nature and mechanism of the action of diuretics.

2 Four different diuretics were administered: salyrgan and merbaphen of the mercurial group, and metaphyllin and theobromine sodium salicylate of the xanthine group. The relationship between the amount of the drug given and the magnitude of the diuretic response was studied.

45 Gamble, J. L., Blackfan, K. D., and Hamilton, B. A Study of the Diuretic Action of Acid Producing Salts, *J. Clin. Investigation* **1**: 359, 1925.

3 The regimen employed afforded sufficient constancy of water and salt metabolism of the body to evaluate the effects of medication. A constant uniform diet and the same measured amounts of water were given at specified times every day throughout these studies. Likewise, specimens of urine were collected at specified times at short intervals during the day.

4 All the diuretics studied caused an increased output of water, sodium, chloride, potassium and calcium. No significant change occurred in the metabolism of phosphate, sulphate, ammonia or total nitrogen.

5 Interpretation of the results on the basis of the salt content of body fluids has been made to gain information as to the source of the increased output of water and inorganic salts following the administration of the diuretics. The relation between the increased amounts of water, sodium, potassium and calcium excreted after a diuretic is approximately the same as that existing in the body fluids. The increased amount of chloride excreted during the periods of diuresis after the xanthine diuretics is likewise approximately the same as that existing in an equivalent amount of body fluid, after the mercurial diuretics the excretion of chloride is somewhat greater.

6 Analysis of the amounts of sodium and potassium excreted on the basis of the concentrations in which they exist in the extracellular and intracellular fluids shows that the diureses represented a predominant loss of extracellular body fluids, the intracellular loss being only 10 per cent or less of the total.

7 The increased amounts of calcium in the urine during diuresis are mainly derived from the body fluids excreted.

8 The water and salts lost from the body in normal subjects during diuresis were regained by a compensatory retention which began immediately on the cessation of diuresis. On the constant dietary regimen employed, the greater the diuresis, the longer was the time necessary for the body to regain its lost fluid.

9 A relationship was evident between the magnitude of the diuretic response and the amount of body fluids available for excretion, i. e., the greatest diuretic response to a given drug was observed in the largest subject.

10 In general, merbaphen produced a slightly greater effect than the same amount of salyrgan, the xanthine diuretics caused a smaller response than a comparable clinical dose of the mercurial diuretics.

11 Doubling the dose of salyrgan and of merbaphen approximately doubled the duration of the diuresis and approximately trebled its magnitude.

12 Neither the xanthine nor the mercurial diuretics caused measurable changes in the specific gravity or in the sodium or chloride contents of the blood serum during the height of, or after, diuresis in these normal subjects. The negative results of these studies are opposed to the opinions of investigators who believe that diuresis following diuretic drugs is initiated by the kidneys in response to measurable changes in some of these constituents in the blood.

13 The rate of glomerular filtration, measured by the method of Rehberg (modified), appeared to be the same during the diureses caused by both the mercurials and the xanthines as it was on the control days. This suggests that the diureses observed in our subjects were not related to changes in the rate of glomerular filtration.

14 The percentage of tubular reabsorption, on the other hand, was always found to be decreased, and the decrease was in proportion to the diuretic effect.

15 The diuretic effects of the various drugs studied were qualitatively similar, the differences being in magnitude and duration rather than in kind.

JERUSALEM ARTICHOKE IN THE TREATMENT OF DIABETES

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The purpose of the experiments was to determine whether the carbohydrate contained in Jerusalem artichoke is more available for the nutrition of certain subjects with severe diabetes than equal quantities of other carbohydrates. Feeding experiments were carried out with two human subjects with severe diabetes and with a completely phlorhizinized dog.

DIABETIC SUBJECTS

CASE 1—R P, a man, aged 38 years, first had symptoms of diabetes at the age of 29 years. The disease had run a rapid course, and to the date of the experiments the patient had had a quantitative diet with insulin for seven years. During this time he had been continuously under the observation of Dr R T Woodyatt, and was an intelligent, trained and experienced patient. His usual diet contained carbohydrate 105, protein 127 and fat 183, on which he remained in good health, but not free from morning glycosuria on an insulin dose of 75 units.

CASE 2—H E, a man, aged 49 years, had had diabetes since the age of 40 and had required treatment with insulin for seven years. This patient was very intelligent and a trained and experienced patient who had been under Dr R T Woodyatt's observation continuously for seven years. His customary diet contained carbohydrate 94, protein 74 and fat 181, with calories 2,301 and an estimated dextrose equivalent of 155 Gm,¹ on which the urine was usually free from sugar with an insulin dosage of 50 units, divided into 40 in the morning and 10 in the evening.

JERUSALEM ARTICHOKE

The product used consisted of dried slices of the tuber *Helianthus tuberosus*. The product was analyzed for carbohydrate by hydrolysis, reduction and polariscopy, for total nitrogen by the Kjeldahl method, for fat by desiccation and extraction by ether, and for water by desiccation and total ash by weight after combustion. Total protein was estimated as $6.25 \times$ total nitrogen. The data obtained are shown in table 1.

Levulose—Weighed parts of the desiccated product weighing from 1 to 20 Gm were hydrolyzed with from 200 to 500 cc of 0.9 per cent hydrochloric acid at water-bath temperature. During the process samples of the hydrolysate were

This investigation was financed by Pabst Dietary Products Inc, of Milwaukee. From the Department of Medicine of Rush Medical College of the University of Chicago and Presbyterian Hospital.

¹ The D, or available dextrose, was calculated by the formula $D = C + 0.58 P + 0.1 F$

drawn off and analyzed at intervals of fifteen minutes to determine the time at which the reducing power had reached a maximum. The maximum was usually reached at the end of two hours and a half, before which hydrolysis was incomplete and after which darkening of the fluid and loss of reduction showed the destruction of some carbohydrate. The hydrolysate was cooled rapidly and was exactly neutralized to litmus while in an ice bath. The portion to be used for polariscopy was cleared with blood charcoal. The reducing power was determined by modification of the Folin colorimetric method for the determination of sugar in the blood. The hydrolysates were always strongly levorotatory. The levorotation and reducing power expressed in terms of levulose are shown in table 2.

TABLE 1—*Analysis of Jerusalem Artichoke*

Analysis	Carbo- hydrate, per Cent	Protein, per Cent	Fat, per Cent	Water, per Cent	Ash, per Cent	Fiber and Undetermined Constituents, per Cent
1	68.2	7.2	0.5	4.0	5.9	
2	68.9	7.4	0.5		5.8	
3	69.9	7.3				
4	69.5					
5	67.4					
6	67.9					
7	70.0					
8	68.6					
9	68.6					
Average	68.8	7.3	0.5	4.0	5.8	13.6

TABLE 2—*Levulose in Hydrolysates of Jerusalem Artichoke*

Analysis	Levulose by Reduction, Gm	Levulose by Polariscopy, Gm
1	5.46	2.0
2	5.51	2.4
3	5.59	2.1
4	5.56	2.2
5	5.39	2.1
6	5.43	2.2
7	5.60	2.0
8	5.49	2.1
9	5.49	2.1
Average	5.50	2.1

As both the levorotation and reducing power disappeared after fermentation with yeast it appeared that a large portion of the reducing substance was levulose. The hydrolysate always gave a strong test for ketoses.

EXPERIMENTS

Experiment 1—Phlorinized Dog—After a dog, weighing 11.5 Kg., had fasted for twenty-four hours, the animal was given 1 Gm. of phlorizin subcutaneously every twenty-four hours during the experiment, which was carried out in eight hour periods. Deglycogenization was accomplished with 0.04 cc. of epinephrine hydrochloride in a 1:1,000 dilution, per kilogram, given every four hours, until the dextrose-nitrogen ratio became constant. The results of the first six periods are shown in table 3.

In periods 3, 4 and 5 the dextrose-nitrogen quotient was constant at an average of 3.03, giving a glycolytic factor for protein for this dog of $3.03/6.25$, or 0.48. During those three periods 32.2 Gm of dextrose was excreted. Allowing for this caloric loss, the animal was given one sixth of its basal caloric requirements as half milk and half 22 per cent cream every four hours.

At the beginning of the fifteenth period the feedings were changed in an attempt to bring about a nitrogen equilibrium. In periods 8 to 12, 107 calories in the form of dextrose was lost in the urine each twenty-four hours. At this time the animal weighed 10.25 Kg. The nitrogen excreted in periods 10 to 12 was 7.8 Gm. Allowing 30 calories per kilogram above the urinary loss of calories as dextrose and adding sufficient casein to give 7.8 Gm of nitrogen each twenty-four hours, the twenty-four hour feeding requirement was calculated as 57 Gm of 33 per cent

TABLE 3—Results of Deglycogenization of Dog During First Six Periods

Period	Feeding	Dextrose in Urine, Gm	Nitrogen in Urine, Gm	D/N
1	0	15.23	1.8	8.46
2	0	10.62	3.1	3.43
3	0	10.40	3.5	2.97
4	0	11.12	3.7	3.00
5	0	11.64	3.7	3.11
6	0	12.80	3.6	3.52

TABLE 4—Results of Deglycogenization of Dog During Seventh to Fourteenth Periods

Period	Feeding $\frac{1}{2}$ Cream, $\frac{1}{2}$ Milk, Gm	Dextrose in Urine, Gm	Nitrogen in Urine, Gm	D/N
7	48 } 48 }	15.51	3.4	4.56
8	Same as 7	12.54	3.1	4.04
9	Same as 7	12.43	2.8	4.44
10	Same as 7	10.80	2.7	4.00
11	Same as 7	9.95	2.6	3.82
12	Same as 7	11.54	2.5	4.56
13	Same as 7	10.53	2.4	4.39
14	Same as 7	9.16	2.5	3.66

cream and 52 Gm of casein. Fifty-nine cubic centimeters of 33 per cent cream was diluted with water to exactly 300 cc. To 50 cc of this diluted cream 8.66 Gm of casein was added, and the mixture was fed every four hours without difficulty.

In periods 17 to 19, or the three periods preceding the feeding of Jerusalem artichoke, the average amount of dextrose excreted per period was 12.35 Gm and the average amount of nitrogen was 3.7 Gm while the average dextrose-nitrogen quotient was 3.32. It will be noted that the diet of cream and casein stabilized the excretion of dextrose and nitrogen.

In period 20, 10 Gm of pulverized dry slices of Jerusalem artichoke were added to each of two feedings.

In period 20, the extra dextrose from artichoke was $15.23 - (3.5 \times 3.32) = 3.61$ Gm, in period 21, $17.39 - (3.9 \times 3.32) = 4.44$ Gm, in period 22, $13.93 - (3.8 \times 3.32) = 1.31$ Gm, making the total extra dextrose excreted 9.36 Gm.

The specimens of urine from periods 20, 21 and 22 were dextrorotatory, and the dextrose value determined polariscopically agreed with that calculated from

reduction determinations The reducing substance was fermented by yeast The average amount of dextrose excreted in each of periods 23, 24 and 25, or the three periods following the feeding of Jerusalem artichoke, was 12.25 Gm, and the average amount of nitrogen was 3.5 Gm The theoretical quantity of dextrose available from 20 Gm of Jerusalem artichoke as calculated from the formula was $D = C + 0.48 P + 0.1 F = 72.4 \times 0.20 = 14.48$ Gm The percentage of the theoretical available dextrose obtained as extra dextrose was $9.36/14.48 \times 100$, or 64.6 per cent This figure is comparable to those obtained by Sansum and Woodyatt,² who found that from 52 to 75 per cent of the feeding was extra dextrose when quantities of from 8 to 16 Gm of pure dextrose were fed

TABLE 5—*Feedings of Dog to Establish Nitrogen Equilibrium*

Period	Feeding		Dextrose in Urine, Gm	Nitrogen in Urine, Gm	D/N
	Cream Mixture, Gm	Casein, Gm			
15	50	8.66	11.69	3.2	3.64
	50	8.66			
16	Same as 15		12.02	3.7	3.25
17	Same as 15		12.19	3.7	3.27
18	Same as 15		12.19	3.7	3.27
19	Same as 15		12.65	3.7	3.42

TABLE 6—*Excretions of Dog During and Following Feeding of Jerusalem Artichoke*

Period	Feeding			Dextrose in Urine, Gm	Nitrogen in Urine, Gm	D/N
	Cream Mixture, Gm	Casein, Gm	Jerusalem Artichoke, Gm			
20	50	8.66	10	15.23	3.5	4.35
	50	8.66	10			
21	50	8.66	0	17.39	3.9	4.46
	50	8.66	0			
22	Same as 21			13.93	3.8	3.66
23	Same as 21			12.29	3.6	3.41
24	Same as 21			12.36	3.5	3.53
25	Same as 21			12.09	3.4	3.56

Experiment 2—Diabetes Mellitus (case 1)—The patient, weighing 69 Kg, was receiving a diet of carbohydrate 82, protein 74 and fat 179, with D 143 and calories 2,233 Thirty-two units of insulin before breakfast, 16 units before the evening meal and 4 units at 3 a m permitted a slight glycosuria during the entire twenty-four hours, without acidosis This diet and the insulin were used in all of the control periods During the feeding periods oatmeal or Jerusalem artichoke, each calculated to produce 23 Gm of available dextrose, was added to this diet, but the dosage of insulin was kept constant Insulin from the same batch was used during the entire experiment To make sure that the daily collections of urine were complete, creatinine determinations were made on each twenty-four hour specimen by the method using picramic acid The urinary dextrose was determined by the Folin-Berglund method and checked by polariscopy, and the total nitrogen was determined by the Kjeldahl process

The average amount of dextrose in the urine for the period preceding the special feedings was 10.62 Gm, and that of nitrogen, 9.3 Gm. Oatmeal calculated to give 23 Gm of available dextrose and 0.8 Gm of nitrogen was added to the diet. The dextrose in the urine rose to an average of 11.27 Gm and the nitrogen to 10.5 Gm. The oatmeal was then removed from the diet and the average amount of dextrose in the urine dropped to 6.76 Gm and that of nitrogen to 10 Gm. During the period when oatmeal was in the diet the average daily increase in the amount of urinary dextrose above the average of the fore and after periods was 2.58 Gm.

The average amount of dextrose excreted in the urine during the period preceding the feeding of Jerusalem artichoke was 9.09 Gm, and that of nitrogen was 11 Gm. Jerusalem artichoke calculated to give 23 Gm of available dextrose was added to the diet. The average daily excretion of dextrose rose to 13.66 Gm and the nitrogen to 11.3 Gm.

The daily specimens of urine during this period were dextrorotatory, and the dextrose value determined polariscopically agreed with that calculated from reduction determinations. The reducing substance was fermented by yeast.

The artichoke was then removed from the diet, and the average amount of dextrose in the urine dropped to 8.21 Gm and that of nitrogen remained at 11.3 Gm. The average daily increase in the urinary dextrose while artichoke was included in the diet was 5.01 Gm. It will be noted that the average amount of dextrose excreted in the periods preceding and following the experiment with oatmeal was 8.69 Gm and in the experiment with artichoke 8.65 Gm.

Experiment 3—Diabetes Mellitus (case 2)—The patient, weighing 60 Kg, was receiving a diet of carbohydrate 92, protein 54 and fat 172, with D 141 Gm and calories 2,132. Thirty-six units of insulin taken before breakfast and 16 units before the evening meal permitted a slight glycosuria during the entire twenty-four hours, without acidosis. Insulin from the same source as that of experiment 2 was used. The experiment was carried out by the same procedure used in experiment 2.

The average amount of dextrose in the urine before the special feedings was 9.42 Gm and that of nitrogen 8.2 Gm. While oatmeal was included in the diet the average amount of dextrose in the urine rose to 17.06 Gm and that of nitrogen to 8.7 Gm. In the period following, the average excretion of dextrose was 7.66 Gm and that of nitrogen 7.9 Gm. The increase in the amount of urinary dextrose when oatmeal was fed was 8.52 Gm.

The average excretion of urinary dextrose of the period preceding the feeding of the Jerusalem artichoke was 6.26 Gm and that of nitrogen 8.8 Gm. During the period when the Jerusalem artichoke was given the average amount of dextrose excreted daily in the urine was 8.47 Gm and that of nitrogen 8.4 Gm. The reducing substance in the urine was here also proved to be dextrose. The average amount of dextrose excreted in the urine in the period following the feeding of oatmeal was 6.98 Gm and that of nitrogen 9 Gm. The increase in the urinary dextrose while artichoke was given was 1.85 Gm.

In another experiment the amount of dextrose excreted in the urine before oatmeal was given was 6.98 Gm and that of nitrogen 9 Gm. During the period in which oatmeal was given the urinary dextrose rose to 11.99 Gm and the nitrogen to 8.9 Gm. In the period following, the urinary dextrose was 4.52 Gm and the nitrogen 8.4 Gm. The increase in the urinary dextrose during the period in which oatmeal was given was 6.24 Gm.

COMMENT

Levulose, calculated from polariscopy, accounted for only 38 per cent of the total quantity calculated from the reduction of a hexose monosaccharide. In the experiment with the phlorhizinized dog the basal caloric and protein replacement was made with cream and casein, which kept the dog in good physical condition during a prolonged experiment of twenty-five eight hour periods. The extra dextrose obtained by feeding Jerusalem artichoke was 64.6 per cent of the theoretical available dextrose, a result comparable to that obtained when pure dextrose is fed.

In experiments 2 and 3 with diabetic subjects a method was developed for the study of the production and utilization of dextrose in food substances. In case 1 the increase in the amount of dextrose in the urine from ingested Jerusalem artichoke was greater than that from an equivalent quantity of oatmeal. In case 2 the increase in the urinary dextrose after ingestion of Jerusalem artichoke was less than that from an equivalent quantity of oatmeal.

CONCLUSION

From these experiments it is concluded that there is no striking difference in the utilization of Jerusalem artichoke in diabetes from that of an equivalent amount of oatmeal.

PHOSPHATASE STUDIES

III SERUM PHOSPHATASE IN DISEASES OF THE BONE INTERPRETATION AND SIGNIFICANCE

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The significance of phosphatase in the physiology of bone has been studied by Robison and his associates and reviewed by Robison¹ and Kay². Kay^{2a} and others³ reported an increase of plasma phosphatase in several diseases of bone. We have also found increases of serum phosphatase when generalized osteoporosis was produced experimentally⁴.

Some of our other experimental results⁵ indicate the untenability of the current view^{1a} that an increase of plasma or serum phosphatase

From the Laboratory Division, Hospital for Joint Diseases

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is "confined almost exclusively to cases of bone disease" However, determinations of serum phosphatase still find their most useful application in the diagnosis of diseases of the bones Variations of serum phosphatase which are not related to bone metabolism will be considered here only incidentally, and will be discussed elsewhere in greater detail

Kay,^{2a} Jenner and Kay^{3b} and others reporting figures for plasma phosphatase in health and disease used Kay's⁶ or Jenner and Kay's^{3b} method of determination The first of these methods yields low values, largely because of the retardation of hydrolysis of the substrate during the forty-eight hour period of incubation, the results obtained by the Jenner and Kay method are low because of the use of glycine to buffer the substrate The ratios of the figures obtained by these investigators for plasma phosphatase in certain diseases of bone to those found for normal adults and children are also incorrect because the analytic errors are disproportionately greater when the plasma phosphatase content is high These and some other errors have been avoided in our method for the determination of serum phosphatase

SCOPE OF INVESTIGATION

We have determined the values for serum phosphatase (1) in normal children and adults and (2) in certain diseases of bone These data have been used (3) to help establish serum phosphatase as an aid in diagnosis and in estimating the effectiveness of therapeutic measures They may also be used as a basis for the consideration of the (4) biologic significance of variations in serum phosphatase in diseases of bone Sufficient data are available in such a form as to realize these purposes Some of the data must be published here in summary (for instance, those on rickets), they will be published later in full detail

Our procedures for determining the inorganic serum phosphate and serum phosphatase have been described⁷ In the cases in which determinations of serum calcium seemed relevant we used a modified form of the Kramer-Tisdall method Serum was obtained after fasting except as otherwise noted

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NORMAL VALUES FOR SERUM PHOSPHATASE⁸

Adults—The serum of members of the laboratory and hospital staff and of several other normal adults, all apparently in good health, averaged 26 units of serum phosphatase per hundred cubic centimeters, 4 units was found in one case and about 15 in two, in the remaining twenty-one analyses the figures ranged between 2 and 35 units per hundred cubic centimeters, which is perhaps the more strictly normal

TABLE 1—Normal Values for Serum Phosphatase

A Adults						B Children						
Case	Age	Sex	Per 100 Cc of Serum			Case	Age	Sex	Per 100 Cc of Serum			
			Phos phorus, Mg	Phos phatase, Units					Cal cium, Mg	Phos phorus, Mg	Phos phatase, Units	
1	16	M	36	16	T*	1	2	F		58	72	T†
2	19	F	39	31	T	2	2	M		45	77	T†
3	19	F	31	22		3	3	F	108	52	58	T†
4	20	F	40	24		4	3	F		39	107	T†
5	22	F	40	23		5	3	F		51	72	T†
6	25	F	36	21		6	3	F		49	78	T
7	26	M	37	30		7	4	F		47	53	T
8	26	M	37	40		8	4	M		43	52	P‡
9	26	M	46	26		9	6	M	100	35	86	T†
10	26	M	35	32		10	6	F	109	52	31	T†
11	27	F	35	21		11	6	M		47	81	T
12	27	M	38	25		12	6	M		43	65	T†
13	27	M	37	29		13	7	M		49	103	T†
14	27	M	34	22		14	8	M	107	44	51	T†
15	28	M	34	27		15	8	F		46	83	T†
16	29	M	38	33		16	9	M	107	43	81	T
17	30	M	38	20		17	9	M		40	76	P
18	30	M	37	15		18	9	M		37	80	P
19	30	M	26	30		19	9	M		42	84	P
20	32	M	34	26		20	10	F		58	60	T
21	34	M	34	35		21	10	F		45	85	T†
22	34	F	29	22		22	11	M	102	53	100	T
23	34	M	42	23		23	12	F	102	49	89	T
24	44	M	30	24		24	12	F		36	114	P
25¶	11	M	33	29		25	13	M	109	43	53	T†
						26	14	M	106	51	131	T
						27	15	F		40	55	P

* Tonsillectomy

† Four hours after a light breakfast

‡ Two hours after a light breakfast

§ Poliomyelitis

|| The high serum inorganic phosphorus in this adult seems to have been due to daily ultra violet irradiation for about five months

¶ A case of sexual precocity, with pubic hair, etc., at 5

range (table 1,A) An average of 3 units (maximum 39, minimum 16) was found in about a hundred miscellaneous hospital patients with a variety of clinical conditions, excluding only known diseases of bone and liver and jaundice, in which the value for serum phosphatase is higher than normal

Children—Young animals of every species which we have studied show higher values for serum phosphatase than adults of the same species^{8c} Table 1,B shows the values found in twenty-seven normal chil-

⁸ Brief summaries were presented at the annual meeting of the American Society of Biological Chemists, April, 1932,^{4b} and were published recently^{7c}

dren Twenty-one, admitted for tonsillectomy and in fair or good condition at the time, showed an average activity of serum phosphatase of 7.2 units per hundred cubic centimeters, in another group six children who had recovered from acute poliomyelitis and were in good health at the time of the test showed an average of 7.7 units per hundred cubic centimeters about six months after paralysis. The two groups are distinguished in table 1,B. The average for the twenty-seven children was 7.3, one low value of 3.1 units was found (child 10), the other values ranged between 5.1 and 13.1 units. The incidence of higher phosphatase values (from 10 to 13 units) was more frequent between the ages of about 10 and 15, and was perhaps related to the onset of puberty at varying chronological ages and to an increased rate of growth and metabolism.

Serum was obtained from about one half of the children after fasting, from the other half, two or four hours after a light breakfast, the averages in each group were similar.

In about three hundred children between 1 and 15 years of age hospitalized for a variety of clinical conditions (excluding anemia, malnutrition, jaundice and known disease of bone) the range of figures for serum phosphatase was approximately the same as in normal children (from 5 to 14 units). The average was about 7.5 units per hundred cubic centimeters. Higher values for infants up to a few months of age, from about 15 to 20 units per hundred cubic centimeters, were found in some hospitalized cases.

It may be noted that our average value for children is 2.7 times our average normal value for adults, while Kay's average for children is about 1.7 times his average value for adults.^{2a}

The figures for the serum inorganic phosphate showed that in only four children (cases 4, 9, 18 and 24, table 1,B) were they lower than the typical values. Even if these cases were eliminated on the assumption that the serum inorganic phosphate indicated some deviation from the strictly normal state, the general average of serum phosphatase would be lowered only slightly, from 7.3 to 7 units.

The correlation between serum phosphatase and age in a group of normal children could have been demonstrated only by studying a much larger group than was feasible. We have, however, demonstrated this correlation in dogs examined repeatedly over a long period. We found a continuous decrease of serum phosphatase with an increase of age^{5f} (after a sharp increase of serum phosphatase during the first forty-eight hours after birth,^{5d} which is apparently due to the unique effect of nursing on the serum phosphatase of the new-born infant rather than to the specific effect of a particular foodstuff^{5c}). It is obviously not feasible to conduct a study of individual children over a long period of time.

Our series of normal subjects and the larger number of hospitalized patients indicate that there is relatively little variation of serum phosphatase between 2 and 10 years of age. There is apparently a temporary rise between the ages of 10 and 15. At the age of 15 or 16, apparently depending on the anatomic stage of development, the serum phosphatase may be as low as 3 units per hundred cubic centimeters (even 1.6 units in case 1, table 1, A) and as high as 10 or 12 units, the latter values being plausibly associated at this age with active growth. The importance of physiologic age in determining the level of serum phosphatase is emphasized by a case of sexual precocity (case 25, listed with the cases of adults).

SERUM PHOSPHATASE IN DISEASES OF BONE

Local Atrophy of Bone—A certain degree of atrophy of bone, a chronic atrophy of inactivity, is found in chronic arthritis and in other

TABLE 2—*Serum Phosphatase in Generalized Osteoporosis*

Case	Sex	Age	Per 100 Cc. of Serum		
			Calcium, Mg.	Inorganic Phosphorus, Mg.	Phosphatase, Units
1	F	50	10.0	3.3	6.6
Three weeks later			9.9	4.1	7.7
2	F	52	10.4	4.1	5.2
3	F	60	9.7	3.8	5.3
4	F	63	9.5	4.0	2.7*
5	F	68	9.1	2.8	2.2*
6	F	66	9.5	4.6	3.7

* Senile osteoporosis

conditions involving a limited use of the extremities. In fourteen young and middle-aged adults with various chronic arthritides, serum phosphatase was at a high normal level, corresponding to slight atrophy of bone. In three cases the serum phosphatase was 5.1, 6.7 and 8.3 units per hundred cubic centimeters, respectively. In two of these pronounced local atrophy was found, we assume that it was present in the third, although the patient did not return for verification. It seems that a systematic study of arthritis from this standpoint (which is now in progress) is justified.

Generalized Osteoporosis—Age is obviously a factor in determining the level of serum phosphatase in generalized osteoporosis. In the middle-aged the serum phosphatase may rise to about twice the normal average, while there is no rise in true senile osteoporosis. These results are in agreement with our observations in experimental osteoporosis. The experimental results also indicate that in young patients suffering from generalized osteoporosis a greater deviation from the normal can be expected. The figures for serum calcium and inorganic phosphorus were normal.

Hyperthyroidism.—In hyperthyroidism a negative calcium balance is sometimes to be expected. It is probable, however, that roentgenologic evidence of this will not always be present. In three patients with a high basal metabolic rate (from +30 to +70 per cent) the serum inorganic phosphorus and serum phosphatase were at the high normal level or higher. Only in one case (1, table 3) was there roentgenographic evidence of osteoporosis.

In a case still under observation, in which the initial basal metabolic rate was about +70 per cent, the serum phosphatase level rose over a period of about five weeks (the successive values being 5, 5.3, 6.2, 7.8 and 10.1 units per hundred cubic centimeters). The serum inorganic phosphorus figures during the same period remained fairly constant at 4.5 ± 0.3 mg per hundred cubic centimeters.

Osteomalacia.—In osteomalacia a high level of serum phosphatase is associated with a low level of serum inorganic phosphorus, as in

TABLE 3—*Serum Phosphatase in Hyperthyroidism*

Case	Sex	Age	Per 100 Cc. of Serum			Comment
			Calcium, Mg	Inorganic Phosphorus, Mg	Phos- phatase, Units	
1	F	41	10.5	4.6	4.8	Basal metabolic rate, +30 per cent osteoporosis, spine and pelvis, sternum deformed
2	F	30	11.1	5.2	4.4	Basal metabolic rate, +70 per cent
3	F	46	10.2	3.7	4.0	Basal metabolic rate, +45 per cent

rickets. In a case of "nontropical sprue" (idiopathic steatorrhea) in a man about 40 years old we had similar results: serum calcium, 7.8 mg per hundred cubic centimeters, serum inorganic phosphorus, 1.9 mg, and serum phosphatase, 8.2 units.

Hyperparathyroidism.—In one case of this relatively rare disease the serum phosphatase was 20.2 units, however, four months after the removal of a large parathyroid adenoma the phosphatase was 13.8 units per hundred cubic centimeters, and eight months after the operation, 12.1 units.⁹ This case was complicated by renal dysfunction. Before operation the serum inorganic phosphorus was 7.1 mg per hundred cubic centimeters, and was associated with 47.6 mg of urea nitrogen per hundred cubic centimeters of blood, 10.1 mg of uric acid and 5 mg of creatinine, figures strikingly similar to those found in the disturbance of renal function in acute experimental hyperparathyroidism in dogs.

9 Our initial observations were made possible through the courtesy of Dr. A. Guttman and Dr. F. M. Hanger of the medical service of the Presbyterian Hospital, New York. We are indebted to Dr. William Barclay Parsons, Jr., of the surgical service of the Presbyterian Hospital, for the opportunity of making the postoperative observations.

The value for serum calcium, 13.1 mg per hundred cubic centimeters, while only moderately high had undoubtedly been depressed by the high level of serum inorganic phosphate. The remarkable clinical improvement after the operation included also improvement in renal function, with a return to normal values for serum inorganic phosphorus, urea nitrogen was 29.3 mg per hundred cubic centimeters of blood, uric acid

TABLE 4—*Serum Phosphatase in Osteomalacia*

	Case	Sex	Age	Per 100 Cc. of Serum		
				Calcium, Mg	Inorganic Phosphorus, Mg	Phosphatase, Units
1		F	20		1.6	10.3
2		F	40	9.5	1.5	11.1

TABLE 5—*Serum Phosphatase in Paget's Disease (Osteitis Deformans)*

Case	Sex	Age	Per 100 Cc. of Serum			Degree of Involvement
			Calcium	Inorganic Phosphorus,	Phos phatase,	
			Mg	Mg	Units	
A Polyostotic						
1	M	55		4.0	15*	
2	F	46	9.6	4.1	50	
3	M	68		2.9	52	
4	F	53	9.5	4.3	69	
5	M	48	9.3	3.5	70	
6	M	63		3.6	74	
7	F	53		3.7	76	
8	M	43	10.8	4.3	107	
9	M	55		4.0	114	
10	M	47	10.0	4.3	125	
B Localized						
11	F	69	10.0	3.5	4.9	Both tibias
12	M	66	9.5	2.5	5.9	
13	M	63	9.6	2.8	5.9	Ilium
14	M	70		3.6	6.6	Ilium, ischium, pubis
15†	F	62	9.2	5.0	10.2	Lower lumbar vertebrae, pelvis, hips
16	F	43	10.4	3.6	10.7	Both tibias
17	F	64	12.4	1.8	11.8	Skull, femur
18	M	56	10.9	3.6	12.0	Femur
19	M	50	10.2	3.4	15.4	Skull, tibia
20	F	52	10.2	3.4	17.2	
21	F	54		3.5	17.7	Pelvis, femur
22	F	50		3.2	17.9	Femur
23	F	56	9.9	3.8	23.1	Tibia, femur

* See text, page 95

† Sister of patient in case 2

6.4 mg and creatinine 2.4 mg, the serum calcium was at a low normal level, 8.9 mg per hundred cubic centimeters

Paget's Disease—In florid polyostotic Paget's disease we have found from 50 to 125 units per hundred cubic centimeters (from 20 to 50 times the normal). In some cases of more or less localized Paget's disease the serum phosphatase was as low as 5 or 6 units per hundred cubic centimeters. Relatively lower values for phosphatase were found in the oldest subjects, in most cases this was undoubtedly due to localized

involvement, in others possibly to considerable spontaneous healing by sclerosis. The tendency to healing by sclerosis is observed in many advanced cases of Paget's disease. In one case (1, table 5, A) repeated analyses yielded consistent results, closely approximating the average figures of 4 mg of inorganic phosphorus per hundred cubic centimeters of serum and 15 units of phosphatase. Postmortem examination confirmed the diagnosis of polyostotic Paget's disease, revealing involvement of the skull, pelvis, femurs, tibiae, right humerus and left ulna, left shoulder girdle and chest¹⁰. Evidence of sclerosis was widespread, which explained the relatively low values for serum phosphatase.

It may be significant that the average age in the polyostotic group was 53 years, as compared with 58 years for the group with localized Paget's disease. Of eight patients over 60 years of age with Paget's disease only two suffered from the polyostotic form (serum phosphatase, respectively, 52 and 74 units) and six suffered from the more localized

TABLE 6—*Age Incidence of Polyostotic and Localized Paget's Disease*

	Average Age	Total Number of Cases	Patients 60 Years and Older	
			Number of Cases	Percentage of Total
Polyostotic Paget's disease	53	10	2	20
Localized Paget's disease	58	13	6	47

involvement (177 units of serum phosphatase in one and from 49 to 118 in the remaining five).

It seems advisable to check in other cases, wherever found, the indicated correlation between age and the incidence of the polyostotic or the more localized forms of Paget's disease. Correlated determinations of serum phosphatase would be useful in this connection.

We may also point out the familial factor in Paget's disease in cases 2 and 15, one patient suffering from the polyostotic form and the other from localized involvement. It seems that the determination of serum phosphatase might offer a means of searching for the earliest evidence of Paget's disease within families in which the disease has been found in one or more of the members.

In a comparison of the analytic values found in hyperparathyroidism and Paget's disease it must be noted in the first place that the serum inorganic phosphorus is typically low in hyperparathyroidism and is frequently at a high normal level or just above it in Paget's disease. In one patient, however, a woman 64 years of age (case 17, table 5), the serum calcium was 12.4 mg per hundred cubic centimeters, the serum inor-

¹⁰ Jaffe, H. L. Paget's Disease of Bone. *Arch Path* **15** 83 (Jan) 1933.

ganic phosphorus 1.8 mg and the serum phosphatase 11.8 units (Somewhat higher value for serum calcium and a lower value for inorganic phosphorus had been previously found in the same case in another laboratory) The chemical findings indicated the possibility of hyperparathyroidism The clinical diagnosis of Paget's disease was supported by the roentgen examination This case was the only one of twenty-three observed by us in which the chemical changes usually associated with hyperparathyroidism were found in a case of Paget's disease While in itself the association of these chemical and roentgenologic findings in the same case is interesting, the rarity of such association emphasizes the lack of basis for assuming hyperparathyroidism to be the etiologic factor in Paget's disease It is well known that secondary enlargement of the parathyroid glands may be produced in experimental rickets and in experimental acidosis, the possibility of some secondary enlargement of the parathyroid glands in Paget's disease might therefore be conceded However, pathologic hyperfunction is not necessarily associated with such secondary enlargement, and if parathyroid hyperfunction is sometimes associated with evidence of Paget's disease the association is rare indeed ¹¹

A consideration of serum calcium, inorganic phosphorus and phosphatase in hyperparathyroidism and Paget's disease must be amplified

11 The belief held in some quarters that parathyroid function is of etiologic importance in Paget's disease is arrived at on the basis of reported observations of enlargement of the parathyroid glands in this condition and of alleged clinical improvement following removal of one or more such parathyroids (Ballin, *M Ann Surg* **96** 649, 1932, J Bone & Joint Surg **15** 120, 1933) Such supposedly enlarged parathyroids are considered to indicate hyperfunction and their removal is therefore considered justifiable by these observers However, when critical judgment is applied to their reasons for calling these parathyroids hyperplastic, it soon becomes evident that there is no convincing basis for such assumption To prove that a parathyroid of an adult is hyperplastic the gland must be fixed in a solution of formaldehyde, cut in frozen sections and stained with a fat stain The presence of large numbers of principal cells containing little or no intracellular fat is at the present time the only valid microscopic evidence of such hyperplasia The assumption of hyperplasia on the basis of increased size (unless this increase is very great) is unjustified, as it is established without doubt that in old and especially in senile persons the parathyroids may be somewhat enlarged even in the absence of osseous disease Furthermore, the quantity of interstitial fat may be increased, and gross enlargement of the gland under such circumstances has no significance whatever Pitted against this clinical and somewhat empiric view of the significance of the parathyroid in Paget's disease is the recent experience of patho-anatomists who have found that in most cases of Paget's disease the parathyroids are in no way abnormal, although they have also observed that mild degrees of secondary hyperplasia may occur On theoretical grounds and on the basis of the present knowledge of the pathogenesis of Paget's disease any improvement that is alleged to follow the operation as such cannot be considered more than temporary, and it certainly does not establish parathyroid dysfunction as of etiologic importance in the disease

by a statement of factors influencing these values and their interpretation. Nephritis, causing a rise of serum inorganic phosphate and a decline of serum calcium, may mask the evidence of these determinations for true hyperparathyroidism. We think it advisable to determine urea or nonprotein nitrogen in all cases in which Paget's disease or hyperparathyroidism is suspected.

Reliance may be placed on the determination of serum phosphatase. The value of serum phosphatase as a criterion of disease of the bone is not impaired in the presence of nephritis. Serum phosphatase is, however, commonly increased in jaundice,^{5b} so that determinations or estimates of the icteric index are desirable, particularly in those cases in which only a moderately high level of serum phosphatase is found. (We believe that the increases of serum phosphatase and of the icteric index represent disturbances of different functions of the liver, and

TABLE 7—*Serum Phosphatase in Osteosclerosis Fragilis Generalisata*

Per 100 Cc. of Serum			Comment
Calcium Mg	Inorganic Phosphorus, Mg	Phosphatase, Units	
10.3	2.3	21.3	Initial analysis
10.3	2.3	21.4	Ten days later
	2.8	16.7	Wedge osteotomy seven days later
	2.3	15.5	Ten days later
			Forty three days later

that increased values of serum phosphatase may be found in disturbances in the liver even in the absence of jaundice^{5c})

Osteosclerosis Fragilis Generalisata (*Albers-Schonberg Disease, Marble Bones*)—In one case of osteosclerosis fragilis generalisata in a youth 16 years of age, the activity of the serum phosphatase was from 2 to 3 times the average value for children and from about 5 to 8 times the average value for adults. We believe that in this case comparison with the adult is justified by the apparent physiologic age of the patient, the value for serum inorganic phosphorus supports this view.

(Osteotomy performed to correct deformities of bones is frequently followed by a decrease of serum phosphatase. This effect was found also after osteotomies performed for the correction of rachitic deformities, as well as in the case cited, and is apparently distinguished by its persistence from temporary postoperative decreases of serum phosphatase which we have observed following other operations. The decrease of serum phosphatase during the healing of an operative defect in abnormal bone seems significant. It suggests that the healing of the defect in some manner partially counteracts the disease process. However, other factors may be involved.)

Infantile Rickets—The correlation of the activity of serum phosphatase with the pathologic process was strikingly indicated during the observation and treatment of a large number of children with rickets¹²

In twenty-seven cases of active infantile rickets the serum phosphatase ranged from 30 to 190 units, about 4 to 25 times the normal average, depending on the severity of the condition. Negro children generally show the higher figures for serum phosphatase, associated with more severe clinical conditions. Previous irregular treatment with cod liver oil or exposure to the sun, particularly during the summer months, may be reflected in a milder clinical condition associated with only a moderately high level of serum phosphatase.

In active rickets, when no treatment was given, and on inadequate treatment, the serum phosphatase frequently continued to rise, when healing was slow on treatment with cod liver oil or small doses of viosterol, the phosphatase decreased slowly, if at all, on larger doses of viosterol, "minimum rapidly effective doses," there was a marked decrease of serum phosphatase within ten days or sooner, the continued rapid decrease of serum phosphatase was associated with other evidence of rapid healing. After treatment, for about two months, the phosphatase values remained constant, generally at a high normal level. The stabilized phosphatase value was reached in advance of the completion of the process of healing. Reconstruction of the bone may not be completed for months, when the reconstruction is complete, the serum phosphatase is within the normal range.

In some cases a diagnosis of rickets was based on the clinical signs (enlargement of the epiphyses, beading of the ribs, etc.) The serum phosphatase was within the normal limits, sometimes at a high normal level, suggesting that while the signs had persisted active rickets was no longer present. Roentgenologic examination confirmed the evidence of the determinations of serum phosphatase.

We shall publish elsewhere a more detailed study of phosphatase in rickets,¹² as the volume of our data does not permit their presentation and discussion at this time.¹³

12 Bodansky, A., and Jaffe, H. L. Phosphatase Studies. V. Serum Phosphatase as a Criterion of the Severity and Rate of Healing of Rickets, *Am J Dis Child*, to be published.

13 After most of our work had been completed, Smith and Maizels^{3c} and Smith^{3d} published their studies of clinical rickets. The average plasma phosphatase in a series of seven normal children was 0.17 unit, in fourteen infants under 1 year, 0.23 unit, and in ten breast-fed infants from 6 to 8 months of age, about 0.25 unit. The maximum value reported in rickets was 1.4 units, or about 8 times the average normal figure in the series in which this value was reported. This was their highest ratio. The determinations were performed by a modification of Kay's method at p_H 7.6 and after incubation for forty-eight hours. We have criticized these conditions on theoretical as well as on practical grounds.^{7c}

Fragilitas Ossium—In two cases (2 and 3, table 8) the values for serum phosphatase were within the normal range. In case 3 the higher level of serum phosphatase possibly associated with this disease of the bones may have been lowered by anemia to the value actually found. In case 4, however, the level of serum phosphatase was definitely high. It seems that a study of special features that may be related to the different individual findings would be justified. In case 5, for instance, the high level of serum phosphatase was definitely related to late rickets (juvenile osteomalacia), which complicated this case. On treatment with viosterol the serum phosphatase level declined (it may be noted that the serum inorganic phosphate remained low).

A familial factor was indicated by cases 1 and 2. The father had the typical blue sclera, although he had never sustained any fractures.

TABLE 8—*Serum Phosphatase in Fragilitas Ossium*

Case	Sex	Age	Per 100 Cc. of Serum			Comment
			Calcium,	Inorganic	Phos	
				Phosphorus,	phatase,	
1	M	35	10.2	2.8	2.4	Father of patient in case 2
2	M	3		4.0	7.0	Recent fracture
3	F	5	10.5	4.8	9.9	Recent fracture, anemia
4	F	5	11.2	4.8	19.1	Recent fracture
5	M	7		1.9	32.4	Late rickets also suggested
			9.8	1.8	35.2	3 years later, definite evidence of late rickets and diabetes insipidus
				1.5	28.7	10 days later, viosterol
				1.4	24.4	9 days later
			10.2	1.8	13.4	7 days later
			11.3	1.4	18.1	6 days later

Fractures—A fracture may be related, in some cases at least, to a preexisting lesion of bone, for example, slight osteoporosis. For this reason it is impossible to conclude with certainty that the slight rise of serum phosphatase which was found in four of thirteen adults (cases 8, 15, 17 and 18, table 9) was due in every case to the fractures. On the other hand, it is suggestive that the four fractures had been sustained forty-two, four, eighteen and twenty-three days before the analyses, respectively, and at least three of them could be termed recent. In case 12, (a fracture 2 days old) the serum phosphatase was 3.5 units per hundred cubic centimeters (table 9).

In thirteen adults the average value was 3.9 units (minimum 2.1, maximum 8.5), which is distinctly higher than the normal average. In case 18 the levels of serum inorganic phosphorus and phosphatase were high twenty-three days after the fracture, three analyses done at intervals showed a regular decline within the next three weeks. The patient was not available for further examination.

A child (case 1) had a low value of 3.9 units per hundred cubic centimeters, associated with anemia, in four other children (cases 2 to 5) the values were substantially normal.

Osteomyelitis—In patients with a destructive lesion like osteomyelitis, when it is moderate in extent and when there is little regeneration

TABLE 9—*Serum Phosphatase After Fractures*

Case	Sex	Age	Per 100 Cc. of Serum			Clinical Notes
			Inorganic		Phos phate,	
			Calcium, Mg	Mg		
1	F	5	10.5	5.4	6.4	Right tibia, nonunion
2	F	6	10.3	4.3	3.9	Neck of humerus (15 days*), anemia
3	F	8		5.2	10.2	Right tibia, nonunion
4	M	11		6.0	6.4	Left humerus
				5.2	6.0	Ten days later
5	M	11	10.3	5.5	8.6	Left elbow (6 days)
6	M	21	10.3	4.9	2.4	Left mandible and humerus (56 days)
7	F	41		4.0	3.1	Surgical neck of left humerus
				5.0	3.4	Eleven days later
8	M	41	9.4	3.9	4.7	Left radius, ilium and wrist (42 days)
9	M	42	10.8	3.8	3.7	Right femur and patella, left tibia and fibula (60 days)
10	F	45	9.7	3.8	3.4	Left humerus, diabetes
11	M	47		2.8	2.3	Right humerus, nonunion
12	M	49		3.3	3.5	Skull, left humerus (2 days)
13	M	50		3.0	3.0	Nonunion
14	F	50	10.5	3.9	3.5	Neck of right femur, nonunion
				4.0	3.3	Sixteen days later
15	F	54		3.8	4.7	Upper third of right humerus (4 days)
16	M	60	10.0	3.2	2.1	Inner end of right clavicle
17	M	62	9.9	3.8	4.3	Right tibia (18 days)
18	F	65		5.3	8.5	Right humerus and radius (23 days)
				5.6	7.0	Five days later
				5.0	6.0	Ten days later
				4.5	5.7	Six days later

* The time elapsed after fracture was sustained has been noted in this and several other cases of "recent fractures."

TABLE 10—*Serum Phosphatase in Osteomyelitis*

Case	Sex	Age	Per 100 Cc. of Serum			Comment
			Calcium, Mg	Inorganic Phosphorus, phatase,	Phos Units	
				Mg		
1	M	5	9.1	4.5	4.6*	Pulmonary tuberculosis, weight, 34 pounds (15.4 kg)
2	F	15		5.1	6.6	Right femur
3	F	10		4.9	8.4	
4	M	17		4.6	3.4	Right humerus
5	M	24	10.6	3.4	2.3	Isthium
6	M	43	10.1	3.3	4.8	Left humerus radius and ulna

* The relatively low serum phosphatase in a child 5 years of age is adequately explained by the evident cachexia.

of bone, it seems that the serum phosphatase remains normal. It is possible that a moderate rise takes place when the lesion is more extensive (case 6, table 10). There seems to be some evidence that unusually high leukocyte counts may be associated with a slight increase of serum phosphatase. We think it desirable to bear this factor in mind in future studies of serum phosphatase in osteomyelitis.

Gaucher's Disease—The serum phosphatase seems to be related to the degree of resorption of bone as well as to the anemic condition of the patient

Cysts of Bone—In one child (case 1, table 12) and four adults with localized cysts of the bones (as distinguished from generalized osteitis fibrosa cystica) the serum calcium, inorganic phosphorus and phosphatase were normal. The serum phosphatase was at a high normal level in cases 2 and 5 and distinctly above normal in case 4

Tumors of Bone (Primary and Metastatic)—Metastatic carcinoma invading bone was associated with a definitely raised serum phosphatase

TABLE 11—*Serum Phosphatase in Gaucher's Disease*

Case	Sex	Age	Per 100 Cc of Serum		Comment
			Inorganic		
			Phosphorus, Mg	Phosphatase, Units	
1	F	26	3.8	4.1	No changes in bone
		(9 weeks later)	3.9	3.5	
2	M	24	3.6	10.1	Resorption, pelvis and femurs
3	M	54	3.1	2.6	No changes in bone
4	F	30	1.7	2.3	No changes in bone
5	M	40	3.9	1.5	

TABLE 12—*Serum Phosphatase in Cysts of Bone*

Case	Sex	Age	Per 100 Cc of Serum			Comment
			Calcium, Mg	Inorganic Phosphorus, Mg	Phos phatase, Units	
1	F	11	9.9	4.5	6.2	Left femur, anemia
2	F			1.5	4.1	Right humerus
			10.3	4.7	3.6	Five days later
3	M	23		3.9	3.3	Left humerus
4	F	46	10.6	3.8	6.0	
5	M	40	10.9	4.0	4.0	

The value for serum inorganic phosphorus was high, the serum calcium was normal (cases 1 and 2, table 13). A patient (case 3) with an undiagnosed metastatic tumor of the bone had a distinctly high level of serum phosphatase.

Osteogenic sarcoma (five cases) generally showed increased values, case 5 (sclerosing osteogenic sarcoma of the right humerus) showed a normal value. In two cases repeated observations were possible. In case 7 a diagnosis of sclerosing osteogenic sarcoma of the left tibia was made at a time when the phosphatase was 8.7 units per hundred cubic centimeters, two years later metastasis to the ribs had occurred and the phosphatase was 7 units. In case 8, under observation for a period of about five months, the phosphatase rose gradually.

In two of three cases of multiple myeloma a high value for serum calcium was found, this is a definite diagnostic sign, requiring differen-

tiation from hyperparathyroidism. In hyperparathyroidism, however, a low level of inorganic phosphorus is typical, while the value for serum phosphatase in one case observed by us was about 8 times the normal. The serum inorganic phosphorus was at the normal level in all three cases. In one case (11) the value for serum phosphatase was low,

TABLE 13—*Serum Phosphatase of Patients with Tumors of the Bone*

Case	Sex	Age	Per 100 Cc. of Serum			Diagnosis
			Calcium, Mg	Inorganic Phosphorus, Mg	Phos- phatase, Units	
1	M	42	10.5	6.0	28.1	Carcinoma with metastases to bones
2	F	38		5.5	9.4	Carcinoma with metastases to lumbar vertebrae, sacrum, iliac bones and eleventh rib on left side*
3	F	40	9.6	3.3	12.0	Neoplasm of neck of right femur with metastases to skull (origin unconfirmed)
4	F	42		3.2	16.6	Osteogenic sarcoma of right femur, metastases to lungs
5	F	32		3.5	3.0	Sclerosing osteogenic sarcoma, right humerus
6	M	60	9.0	3.0	7.0	Osteogenic chondrosarcoma, right ilium
7	M	18	11.4	4.2	8.7	Sclerosing osteogenic sarcoma, left tibia
8	F	20 17	10.6	4.0	7.0	Two years later, metastases to ribs
				4.5	6.4	Osteogenic sarcoma
				4.0	5.6	Seventy nine days later
				3.8	6.7	Forty one days later
				3.8	7.1	Seven days later
9	M	42	9.1	4.0	8.2	Thirteen days later
				3.1	4.5	Recurring osteochondromas, left hip
				3.1	4.8	Multiple myeloma
10	M			3.1	4.8	Multiple myeloma
11	F	60	13.2	4.0	1.8	Multiple myeloma
12	M	40	16.1	3.4	4.9	Multiple myeloma
13	M	13		4.0	7.3	Medullary sarcoma (Ewing's tumor), spine and ribs, anemia
14	F	8		4.9	6.3	Medullary sarcoma (Ewing's tumor), left humerus, anemia
						Three months later
15	F	33	11.2	5.4	4.6	Giant cell tumor†
16	F	21	10.1	3.8	4.4	Giant cell tumor, right femur
17	M	16	10.4	4.7	2.9	Giant cell tumor removed ten weeks before, healing anemia
18	M	50	10.8	4.9	3.6	Twenty six days later
			9.3	3.0	4.3	Chordoma

* In a patient studied after this paper was completed (a woman 37 years of age) the initial serum phosphatase value was 56 units per hundred cubic centimeters, serum inorganic phosphorus, 4.9 mg, and serum calcium, 9.8 mg. Seven days later the serum phosphatase rose to 83 units, confirmed by a value of 85 units fifteen days later. There was no clinical evidence of Paget's or Recklinghausen's disease. A suspicion of multiple myeloma seemed to be ruled out by the serum calcium and phosphatase values. The chemical findings indicated a severe and progressive involvement of the bones, necropsy revealed an extensive sclerosing metastatic carcinoma involving practically all the bones of the skeleton. The primary lesion was in a bronchus and was not apparent clinically.

† See text, page 103

in the two others it was about twice the normal average, and therefore lower than in hyperparathyroidism.

In two children with medullary sarcoma the serum phosphatase was normal, however, moderate anemia was present and no doubt masked the effect of the lesion of the bone.

In one case of giant cell tumor, and in another case after extirpation of a giant cell tumor, the serum phosphatase was normal (cases 16 and 17), in a third case presenting a giant cell tumor in one bone (diagnosis

confirmed) and an unidentified lesion in another bone (case 15) the serum phosphatase was slightly raised. Multiple giant cell tumors suggest hyperparathyroidism, however, the suspicion of Recklinghausen's disease was not supported in this case by other findings.

In chordoma (case 18) the serum phosphatase was slightly raised.

A better understanding of the significance of serum phosphatase in tumors of bone may be obtained after a comparison with the serum phosphatase in tumors without involvement of bone or liver, as a species

TABLE 14—*Serum Phosphatase of Patients with Tumors Not Involving Bone*

Case	Sex	Age	Per 100 Cc. of Serum		Diagnosis
			Inorganic Phosphorus, Mg	Phosphatase, Units	
1	F	45	3.7	2.7	Carcinoma of the thyroid
2	F	70	2.7	4.0	Carcinoma of the bladder, uremia, anemia
3	M	71	4.7	3.5	Adenocarcinoma of prostate gland
4	M	55	3.7	2.3	Large adenocarcinoma (?) in epigastric region
5	F	43	3.0	3.1	Metastatic tumor
6	M	47	2.8	2.3	Cystic adenoma of thyroid
7	F	30	4.2	3.2	Cystic adenoma of thyroid
8	F	41	3.3	3.0	Multiple fibromas of uterus and appendix
9	M	35	4.3	2.8	Liposarcoma, postoperative analysis
10	M	66	3.5	3.3	Myxochondrosarcoma
11	F	34	2.3	4.0	Undiagnosed
12	M	53	3.2	5.9	Large spindle cell sarcoma, anemia, icteric index, 5
13	F	50	2.5	6.9	Spindle cell fibrosarcoma, possible metastases to liver, icteric index, 61

TABLE 15—*Serum Phosphatase in Calcinosis Universalis*

Case	Sex	Age	Per 100 Cc. of Serum		
			Calcium, Mg	Inorganic Phosphorus, Mg	Phosphatase, Units
1	F	29	9.2	3.8	3.1
2	F	30		3.9	3.1
				3.4	3.0

of control (table 14). In these cases serum phosphatase seems to be substantially normal, from 2.7 to 4 units. In two cases of spindle cell sarcoma (cases 12 and 13, table 14) the serum phosphatase was 5.9 and 6.9 units per hundred cubic centimeters respectively. The icteric index in case 12 was, however, slightly higher than normal, while it was very high in case 13, in which there was suspicion of metastases to the liver.

Calcinosis Universalis—Because of an assumed relation of this disease to calcium metabolism, the serum phosphatase was determined in two cases. Normal values were found.

Disturbances of Growth—Serum phosphatase was only slightly raised in a case of acromegaly in a man, 50 years of age, the serum cal-

cium was 9.2 mg per hundred cubic centimeters, the serum inorganic phosphorus 4 mg and the serum phosphatase 4.9 units. In three cases of achondroplasia (two children and one adult) no clear shift of serum phosphatase from the normal was seen. The low normal phosphatase in the one adult is probably not related to achondroplasia, slight anemia was found, but its effect on the serum phosphatase cannot be affirmed with certainty in this case.

In one case of cretinism, in a girl about 4 years old, the initial serum inorganic phosphorus and phosphatase were 3.8 mg and 5.3 units per hundred cubic centimeters, respectively. After twenty-one days of treatment with thyroid extract, the serum inorganic phosphorus was 5.3 mg per hundred cubic centimeters and the serum phosphatase, 7.3 units. In a case of mongolism, in a girl about 2 months of age, 6.6 mg of inorganic phosphorus and 7 units of phosphatase per hundred cubic centimeters of serum were found. In a case of amaurotic idiocy, in a boy

TABLE 16—*Serum Phosphatase in Achondroplasia*

Case	Sex	Age	Per 100 Cc. of Serum			Comment
			Calcium, Mg	Inorganic Phosphorus, Mg	Phos phatase, Units	
1	F	49	9.9	4.0	1.4	Slight anemia
2	M	9	10.4	4.7	8.0	Growth retarded at 13 months
3	F	7	10.8	5.1	6.3	Growth retarded at 3 years

2 years of age, 10.8 mg of calcium, 5 mg of inorganic phosphorus and 6.3 units of serum phosphatase per hundred cubic centimeters of serum were found.

CLINICAL INTERPRETATION OF VALUES FOR SERUM PHOSPHATASE

With the qualifications to be stated, our data may serve as an aid to a clinical interpretation of analyses of serum phosphatase. The values in polyostotic Paget's disease and rickets are characteristically high. In the latter, clinical improvement is unmistakably reflected in the decline of serum phosphatase; we believe that no suggested treatment of Paget's disease may be considered effective until the alleged improvement has been shown to be associated with a decrease of serum phosphatase. Osteoporosis (except senile osteoporosis), osteomalacia, hyperparathyroidism and certain malignant tumors of bone (primary or metastatic) are associated with definitely increased serum phosphatase. In various other diseases of bone the level of serum phosphatase, while not equally high, is significantly above the normal.

Other findings will necessarily affect the interpretation of serum phosphatase as an indication of involvement of bone. It is always necessary to consider such factors as senility, malnutrition and anemia, which lower the serum phosphatase, and jaundice and latent jaundice, as

well as involvement of the liver without jaundice, which may raise it. Chemical findings other than serum phosphatase (serum calcium, inorganic phosphorus, urea, nonprotein nitrogen, etc.) must also be considered. We need but mention the basic importance of clinical signs and symptoms, roentgen examinations, etc.

It must be noted particularly that moderately increased activity of serum phosphatase (from 4 to 14 units per hundred cubic centimeters in adults) is found also in catarrhal jaundice, in jaundice due to cinchophen poisoning and to asphenamine intoxication, in cholecystitis with jaundice, in hepatitis, in tumors involving the liver and in some cases of anemia with a high icteric index^{5b}. These conditions must be ruled out before one may infer from increased serum phosphatase that disease of bone is present. We have not found values of 5 units or higher in adults without evidence of involvement of bone or the liver. We are, indeed, inclined to regard any authentic value higher than 4 units as possibly abnormal.

In children, jaundice was associated with high, and anemia and cachexia with low values for serum phosphatase.

The effects of jaundice, anemia and cachexia on serum phosphatase were shown in the absence of disease of the bone.

SIGNIFICANCE OF VARIATIONS IN SERUM PHOSPHATASE

Robison showed that "the production of this enzyme [bone phosphatase] forms a part of cellular activities leading to the formation of bone"^{1a}. Kay explained the high plasma phosphatase in diseases of bone by leakage "at more than the normal rate, possibly because it is produced in excessive amount in the bones in attempted compensation for the lesion, or possibly because owing to weakness of the bones there is a greater amount of bending and crushing which mechanically squeezes out some of the cell contents"^{2a}.

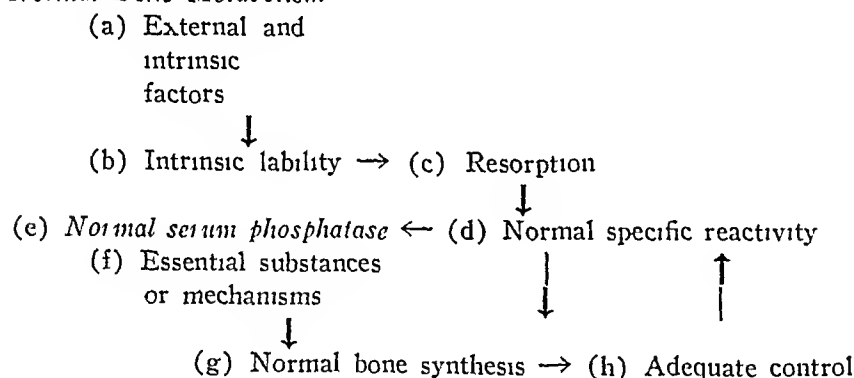
These explanations fail, in their present formulation, to explain in a consistent manner the differences between serum phosphatase in various normal and pathologic states. The higher serum phosphatase of the young is indeed likely to be due to the greater "cellular activities leading to the formation of bone." However, this explanation does not cover the increase of serum phosphatase to the extremely high levels found in rickets or in Paget's disease, the difficulty is increased when the return to normal values after effective therapy is to be explained. The absence of an adequate explanation of the latter has been responsible for unjustified skepticism concerning not only the theories of the significance of serum phosphatase but also its value as an aid in diagnosis.

A formulation is required that would resolve these difficulties and that could be applied to variations in serum phosphatase in both normal and pathologic metabolism and in the course of effective therapy.

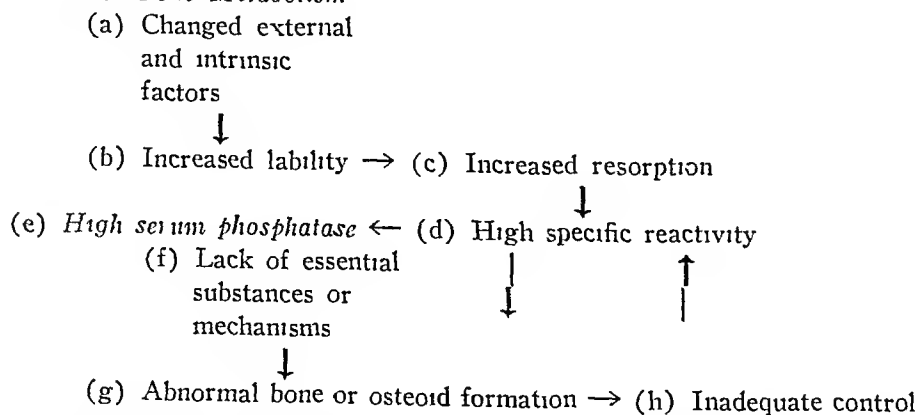
It may be suggested by way of an approach to such formulation, that variations in serum phosphatase, so far as they are related to bone metabolism, are an expression not of "cellular activities leading to the formation of bone," but rather of the "specific reactivity of bone," that is, its capacity for "cellular activities." This specific reactivity may be assumed to be a property of living bone at all times, even when normal cellular activities are rendered impossible for lack of suitable substances or because of the failure of necessary mechanisms. Furthermore, by analogy with the controls that maintain all metabolism at certain equilibriums, it is held that similar controls or inhibitions of the specific reactivity of bone are set up in the course of normal synthesis of bone, when normal synthesis does not occur, these controls are absent or inadequate, and specific reactivity is correspondingly higher, a high level of serum phosphatase is one expression of the high specific reactivity, and formation of normal bone (or osteoid) may be another. Inhibition of specific reactivity increases with age¹⁴

The Manner in Which Serum Phosphatase Is Controlled in Normal and Abnormal Bone Metabolism

Normal Bone Metabolism



Abnormal Bone Metabolism



¹⁴ Carrell, A., and Ebeling, A. H. Age and Multiplication of Fibroblasts, *J. Exper. Med.* **34** 599 (Dec.) 1921

The nature of the particular substance or mechanism that may be lacking for the normal synthesis of bone in a given disease of the bones is apparently of great importance. Deficiency of vitamin D (in clinical rickets) and the unknown etiologic factor of Paget's disease are apparently associated in severe cases with excessive syntheses of osteoid and of abnormal bone, respectively, and with very high values for serum phosphatase. On the other hand, in dietary calcium-phosphorus imbalance the moderately high phosphatase indicates specific reactivity to resorption of bone controlled at a moderately high level.

The decrease of serum phosphatase to normal after effective therapy in diseases of bones may be explained, somewhat schematically, as follows: substances or mechanisms necessary for normal synthesis of bone have been supplied, normal syntheses of bone consequently take place, these lead in turn to the appearance of inhibitions of specific reactivity, specific reactivity controlled at the successively lower levels is expressed by successively lower phosphatase values, when normal specific reactivity is reached, it is expressed by normal serum phosphatase.

COMMENTS

Our view of serum phosphatase as an expression of the "controlled specific reactivity" of bone may be verified by relating the known facts of bone metabolism in health and disease to the corresponding values for serum phosphatase.

In the normal young animal, bone is normally more labile, more susceptible to resorption, than in the adult. The production of experimental rickets in young animals is facilitated by this greater lability. The successful use of young animals in producing experimental hyperparathyroidism was based on the same principle,¹⁵ it is also significant that

15 Bodansky, A., Blair, J. E., and Jaffe, H. L. Serum Calcium and Phosphorus of Guinea-Pigs After Administration of Single and Repeated Doses of Parathormone, *Proc Soc Exper Biol & Med* **27** 708 (April (1930)), Experimental Hyperparathyroidism in Guinea-Pigs Leading to Ostitis Fibrosa, *J Biol Chem* **88** 629 (Oct) 1930. Jaffe, H. L., Bodansky, A., and Blair, J. E. Production in Guinea-Pigs of Fibrous Bone Lesions with Parathyroid Extract, *Proc Soc Exper Biol & Med* **27** 710 (April) 1930, Influence of Age on the Effect of Parathormone on Guinea-Pig Bones, *ibid* **28** 174 (Nov) 1930, Fibrous Osteodystrophy (Ostitis Fibrosa) in Experimental Hyperparathyroidism of Guinea-Pigs, *Arch Path* **11** 207 (Feb) 1931, The Influence of Age and of Duration of Treatment on the Production and Repair of Bone Lesions in Experimental Hyperparathyroidism, *J Exper Med* **55** 139 (Jan) 1932. Jaffe, H. L., and Bodansky, A. Experimental Ostitis Fibrosa Cystica in Dogs, *Proc Soc Exper Biol & Med* **27** 795 (May) 1930, Experimental Fibrous Osteodystrophy (Ostitis Fibrosa) in Hyperparathyroid Dogs, *J Exper Med* **52** 669 (Nov) 1930. Bodansky, A., and Jaffe, H. L. Experimental Chronic Hyperparathyroidism in Dogs Without Hypercalcemia, *Proc Soc Exper Biol & Med* **27** 797 (May) 1930, Parathormone Dosage and Serum Calcium and Phosphorus in Experimental Chronic Hyperparathyroidism Leading to Ostitis Fibrosa, *J Exper Med* **53** 591 (May) 1931.

the zones of most active growth were most actively resorbed¹⁶ Young animals are also more susceptible to the effects of a dietary deficiency in calcium and experimental acidosis¹⁷ However, the greater specific reactivity of the normal young to resorption of bone is controlled at its relatively high level, remaining within certain limits, leading to a higher serum phosphatase on one hand and to growth of bone on the other

In normal adults lower specific reactivity (to slower resorption) involves both slower normal formation of bone and a relatively lower level of serum phosphatase than in children, whereas in senility slow resorption occurs, but specific reactivity is relatively slight,¹⁴ both synthesis of bone and serum phosphatase are at their lowest

In osteoporosis specific reactivity is stimulated in accordance with the degree of resorption, however, as is obvious, synthesis of bone is inadequate because of the lack of an essential substance or mechanism, adequate controls are therefore not set up, and serum phosphatase increases—most in the young, moderately in the middle-aged and slightly or not at all in the senile

In hyperparathyroidism the generalized resorption of bone stimulates specific reactivity However, the virtual calcium-phosphorus imbalance of the hyperfunction permits only relatively slight bone or osteoid synthesis The controls are therefore inadequate, and serum phosphatase rises The resorption in hyperparathyroidism being more active than in generalized osteoporosis, specific reactivity and serum phosphatase are controlled at a higher level

In Paget's disease the typical mosaic structure of the newly formed bone indicates rapid transformation of bone¹⁰ The inorganic serum phosphate in the florid cases is frequently near the upper limit of normal, widespread resorption stimulates cellular activity, but, as has been stated, the newly formed abnormal bone cannot set up adequate controls of specific reactivity, the rapid rate of abnormal formation of bone and extremely high serum phosphatase correspond to the thus inadequately controlled specific reactivity (outline) Senility seems to be a factor in Paget's disease, the oldest patients showing the lowest values for serum phosphatase, in part probably owing to localized

16 Jaffe, H L , Bodansky, A , and Blair, J E Rate of Decalcification and the Sites of Bone Lesions in Experimental Hyperparathyroidism, *Proc Soc Exper Biol & Med* **28** 793 (Jan) 1931, The Sites of Decalcification and of Bone Lesions in Experimental Hyperparathyroidism, *Arch Path* **12** 715 (Nov) 1931

17 Jaffe, H L , Bodansky, A , and Blair, J E The Effects of Parathormone and Ammonium Chloride on the Bones of Rabbits, *J Exper Med* **55** 695 (May) 1932 Jaffe, H L , Bodansky, A , and Chandler, J P Ammonium Chloride Decalcification, as Modified by Calcium Intake The Relation Between Generalized Osteoporosis and Ostitis Fibrosa, *ibid* **56** 832 (Dec) 1932, footnote 4

involvement and spontaneous healing by sclerosis,¹⁰ but in part, possibly, because of the lower specific reactivity of the old

In active rickets normal synthesis of bone does not take place, adequate controls of specific reactivity are therefore not set up, excessive formation of osteoid and high values for serum phosphatase are expressions of specific reactivity controlled at a very high level. Effective therapy results in normal synthesis of bone, so that more adequate controls appear and the decrease of serum phosphatase expresses the specific reactivity controlled at successively lower levels. During reconstruction of the bone the serum phosphatase may remain at a high normal level, but when reconstruction is complete the serum phosphatase is within the normal range.

Osteomyelitis causes no marked rise of serum phosphatase. In the case of such destructive lesions, the principle that applies could probably be expressed as follows. Necrotic bone is not capable of reactions leading to an increased serum phosphatase. New formation of bone, when it occurs, may cause a rise of serum phosphatase. Leukocytosis *per se* may cause a slight rise of serum phosphatase, which is of course not related directly to metabolism of bone.

In experimental acidosis and deficiency in calcium the negative balance is due to a relative increase of resorption and a decrease of normal synthesis of bone, the former stimulates and the latter fails to control specific reactivity adequately. Specific reactivity and serum phosphatase are therefore controlled at a higher level.

SUMMARY

1 Serum phosphate is of diverse origin (from bone, the liver, etc.). The normal range of serum phosphatase in adults is between 1.5 and 4 units per hundred cubic centimeters (average about 2.5) and in children between 5 and 14 (average about 7). Higher values are found clinically in involvements of the bone and liver, lower values, in anemia and cachexia. When serum phosphatase is to be used as an aid in clinical diagnosis of diseases of the bone it has been shown that involvement of the liver with or without jaundice must be ruled out, and when serum calcium and determinations of inorganic phosphate are also to be considered, renal involvement must be eliminated.

2 Destruction of bone *per se*, unless accompanied by new bone or osteoid formation, is probably not associated with a marked rise of serum phosphatase.

3 In diseases of bone serum phosphatase is highest when it is associated with excessive formation of abnormal bone (polyostotic Paget's disease) and with excessive formation of osteoid (rickets). Successful therapy in rickets and hyperparathyroidism resulted in a lowering of the

level of serum phosphatase In Paget's disease spontaneous healing by sclerosis was associated with relatively low values for serum phosphatase Localized Paget's disease (and a moderately high level of serum phosphatase) was relatively more frequent in patients over 60 years of age

4 The use of determinations of serum phosphatase as a criterion of effective therapy in rickets and healed rickets, and in the differential diagnosis of Paget's disease, Recklinghausen's disease, multiple myeloma and tumors of the bone has been discussed

5 Variations in serum phosphatase, so far as they may be related to bone metabolism, are assumed to be an expression of "controlled specific reactivity" to resorption of bone (normal and pathologic) The mechanism by which the specific reactivity of bone and the level of serum phosphatase are controlled at normal or high levels has been suggested

6 Clinical and experimental studies are suggested in connection with the changes in the bones in arthritis, fragilitas ossium, fractures and similar conditions

FURTHER OBSERVATIONS ON THE EFFECT OF DRUGS ON INDUCED CARDIAC STANDSTILL

EFFECT OF EPINEPHRINE AND RELATED COMPOUNDS

M H NATHANSON, M D

MINNEAPOLIS

The heart possesses several important properties. The function most familiar to the clinician is contractility which, when impaired, leads to the frequently observed slow cardiac failure. Sudden cessation of the cardiac activity, however, results from disturbance in another essential property of the heart, that of stimulus formation, termed rhythmicity or automaticity. Normally the sinus node produces the stimulus necessary for cardiac contraction, and the activity of the heart abruptly ceases if this or other rhythmic centers fail to function. Absence of an impulse-initiating mechanism is the cause of the ventricular standstill in complete heart block. The frequency with which impairment of the rhythmic function occurs in other clinical conditions is uncertain, but it probably plays a part in the sudden cardiac arrest occasionally observed on the operating table. The success with which intracardiac injection has resuscitated the asystolic heart in shock, asphyxia and various types of poisoning indicates that the abnormal physiologic mechanism may be present in a variety of clinical conditions.

Previous studies concerned with the effect of drugs on the impulse-initiating property of the heart consist of observations in the experimental animal in which total cardiac standstill has been produced by elimination of the normal pacemaker, or ventricular standstill by the induction of heart block. Clinical studies consist of reports on the response of the asystolic heart to various types of intracardiac injections and on the effect of drugs in the prevention of Adams-Stokes seizures of heart block. These methods have not resulted in a general agreement as to the efficiency of drugs in the prevention and treatment of cardiac standstill.

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Read before the Section on Pharmacology and Experimental Therapeutics at the Eighty-Fourth Annual Session of the American Medical Association, Milwaukee, June 14, 1933

In 1866 Czermack¹ demonstrated that digital pressure on the neck in the region of the vagus nerve causes a slowing of the cardiac activity. The observations of Hering² indicated conclusively that this phenomenon is not due to a direct stimulation of the vagus nerve but is the result of a reflex which originates in a specialized portion of the internal carotid artery, the carotid sinus. In many persons, apparently owing to an overactivity of the vagus nerve,³ prolonged cardiac standstill may be induced. Electrocardiographic observations indicate that the standstill is due to a temporary inactivity of the sinus node and to failure in the formation of secondary centers of impulse initiation. In previous reports⁴ it was pointed out that these subjects permit a direct and well controlled method for the study of the effect of drugs on the

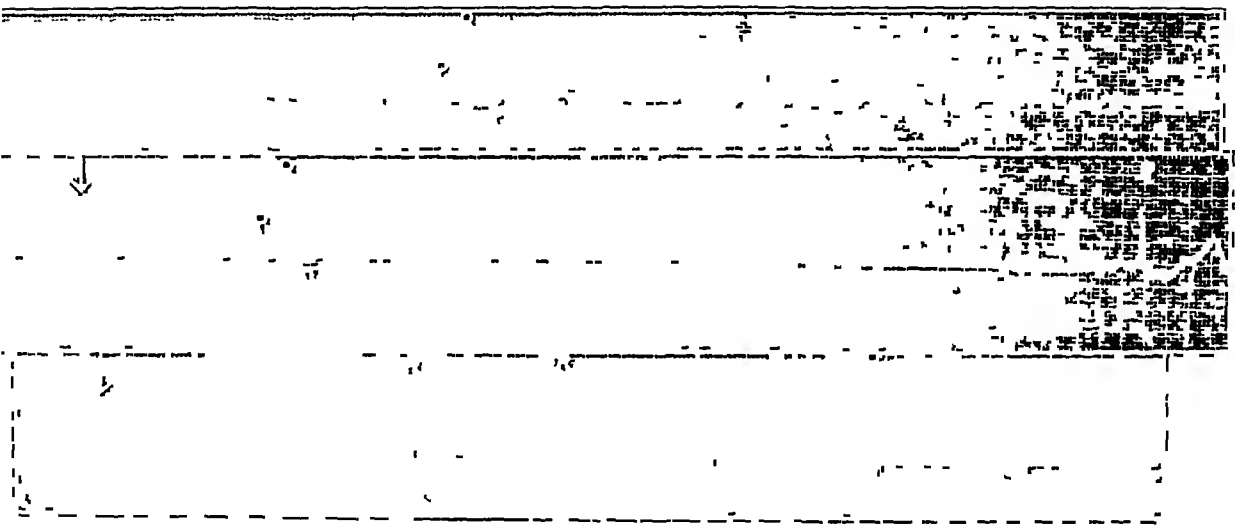


Fig 1 (H B) —A, lead II before pressure on the carotid sinus. B, the effect of pressure on the right carotid sinus is indicated by the arrow. There is a cardiac standstill of seven and one-half seconds. C, compression of the right carotid sinus after administration of 1 cc of epinephrine (1:1,000). Note the alteration in the ventricular complexes and the absence of the P wave starting at X, indicating the development of a ventricular rhythm.

impulse-initiating property of the heart. The evidence that a drug increases cardiac rhythmicity is the prevention of cardiac standstill by

1 Czermack, J. N. Ueber mechanische Vagusreizung beim Menschen, *Jena-ische Ztschr f Med u Naturw* 2:384, 1866.

2 Hering, H. E. Die Karotissinus-Reflexe auf Herz und Gefasse, Dresden, Theodor Steinkopff, 1927.

3 Nathanson, M. H. Site of Hypersensitiveness of the Exaggerated Sinus Caroticus Reflex, *Proc Soc Exper Biol & Med* 29:1037, 1932.

4 Nathanson, M. H. A Method for the Study of the Rhythmic Property of the Human Heart, *Proc Soc Exper Biol & Med* 30:967, 1933. Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, *Arch Int Med* 51:387 (March) 1933.

the formation of a new impulse-initiating center during the period of inactivity of the sinus node

Observations on the effect of drugs on this type of standstill were carried out on a number of suitable subjects, most extensively on one patient (H B) who was especially favorable for this type of study. He was an elderly man in whom an exaggerated response to pressure on the carotid sinus could be obtained with remarkable ease and with only slight discomfort. Moderate compression of the carotid sinus elicited a standstill varying from seven to nine seconds (fig 1 B) which could be repeated with great consistency over a long period of time. In numerous control records there was no indication of a contraction from an ectopic focus during the period of stimulation of the sinus carotid. Similar control studies were carried out on other subjects. Each experiment consisted of a control electrocardiogram recording the effect of pressure on the right carotid sinus. The drug was then administered, and records were taken after suitable intervals, again observing the effect of stimulation of the carotid sinus. The present report consists of the results obtained by this method with (1) a group of drugs selected because they have been suggested in the treatment or prevention of cardiac standstill, and (2) a group of substances which are related in chemical structure to epinephrine. The first group includes epinephrine, ephedrine, barium chloride, calcium gluconate, digitalis, caffeine, coramin, metiazol and thyroxine.

DRUGS SUGGESTED IN THE TREATMENT OR PREVENTION OF CARDIAC STANDSTILL

Epinephrine—Rothberger and Winterberg⁵ demonstrated that in the experimental animal stimulation of the left sympathetic nerve or the administration of epinephrine prevents the cardiac standstill produced by stimulation of the vagus nerve. Cullis and Tribe⁶ showed that this drug increases both the auricular and the ventricular rate in experimental heart block. Since 1916 epinephrine has been used in heart block, usually with favorable results, although apparent ineffectiveness has also been reported. Epinephrine was studied in eight subjects by the present method, and in every case 1 mg. of epinephrine administered subcutaneously abolished the cardiac standstill by the initiation of a ventricular rhythm (fig 1).

Ephedrine—Several observers have reported favorable results in the prevention of Adams-Stokes seizures of heart block by the oral

5 Rothberger, C. J., and Winterberg, H. Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachykardie durch Accelleransreizung, Arch f d ges Physiol **142** 461, 1911.

6 Cullis, W. E., and Tribe, E. M. Distribution of Nerves in the Heart, J Physiol **46** 141, 1913.

administration of ephedrine⁷ Cheer, Tung and Bien,⁸ however, reported no increase in ventricular rate in a case of complete heart block after the administration of 150 mg of ephedrine by mouth. In H B large doses of this drug administered orally and subcutaneously were without effect on the cardiac arrest. In another subject 30 mg of ephedrine was ineffective by intravenous injection, but thirty minutes later 0.1 mg of epinephrine abolished the standstill. This suggested some qualitative difference in the action of the two related substances, but later studies indicated that the differences were entirely quantitative and that an insufficient dosage of ephedrine had been used. In H B 50 mg of ephedrine given intravenously was without effect, but when

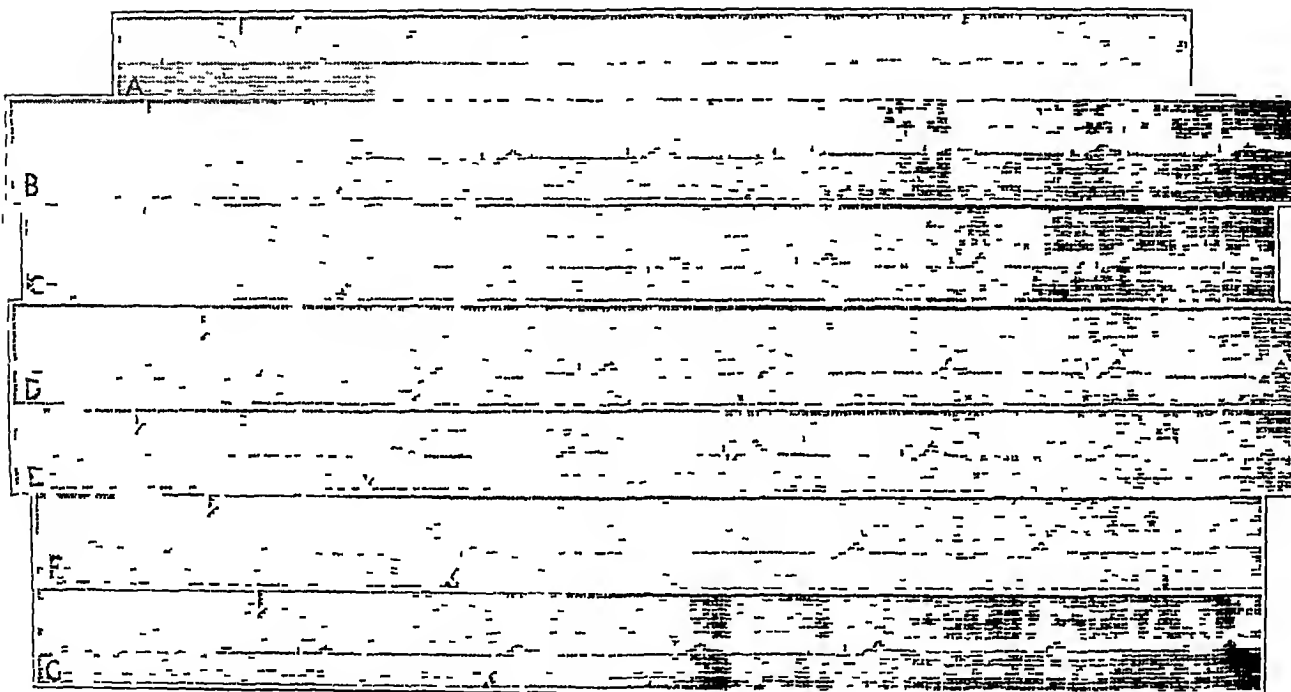


Fig 2 (J C) —A shows a cardiac standstill of six and two-tenths seconds on pressure on the right carotid sinus, indicated by the arrow. B, a tracing made after the intravenous injection of 50 mg of ephedrine sulphate, shows a ventricular rhythm starting at X with pressure on the carotid sinus. C, taken one hour after the injection, still shows an active effect.

the dose was increased to 100 mg a reaction similar to that produced by epinephrine was obtained. More recently two other subjects were

⁷ Miller, T G. A Consideration of the Clinical Value of Ephedrine, *Am J M Sc* **170** 157, 1925. Fahr, George. personal communication to the author. Hollingsworth, M. Ephedrine in Adams-Stokes Syndrome, *California & West Med* **26** 802, 1927. Stecher, R M. A Note on Adams-Stokes Disease Treated with Ephedrine, *Am Heart J* **3** 567, 1928. Wood, J E, Jr. Ephedrine in Adams-Stokes Syndrome, *J A M A* **98** 1364 (April 16) 1932.

⁸ Cheer, S N, Tung, C L, and Bien, C W. Combined Effect of Ephedrine and Atropine on Complete Heart Block, *Am Heart J* **8** 400, 1933.

available, and in both 50 mg of ephedrine by intravenous injection was effective (fig 2) In three subjects it was possible to compare the reactions of epinephrine and ephedrine, this will be reserved for a later portion of this report

Barium Chloride and Calcium Gluconate—The work of Rothberger and Winterberg⁹ indicates that salts of barium and calcium increase the rhythmicity of the ventricles and that with large doses various types of ventricular rhythm occur to the point of ventricular fibrillation These experiments formed the basis for the use of barium chloride in clinical heart block⁹ The drug has been used with apparent benefit in the prevention of the Adams-Stokes seizures, but unfavorable reports also appear in the literature¹⁰ Barium chloride was used in two cases in doses of from 200 to 250 mg a day by mouth In one patient the drug had no effect on the induced cardiac standstill In another subject, J M, the cardiac arrest was prevented by the development of an idioventricular rhythm Large oral and intravenous doses of calcium gluconate had no effect

Digitalis—It is well known that digitalis administered in large doses increases the irritability of the ventricles as evidenced by the occasional development of ventricular extrasystoles and tachycardias It was repeatedly demonstrated in H B that daily doses of 0.2 Gm of digitalis definitely increased the duration of the standstill up to fifteen or sixteen seconds When administered in these doses the drug did not increase the irritability of the ventricles sufficiently to bring about development of an ectopic rhythm The prolongation of the standstill may be explained by the increased sensitivity of the vagus nerve which is one of the effects of digitalis The absence of an idioventricular rhythm agrees with the observations of Schwartz¹¹ who showed that augmentation of the automatic ventricular rate in complete heart block occurs only with toxic doses of digitalis

Caffeine—Von Egmond¹² observed a transient increase in the ventricular rate in experimental heart block after the administration of caffeine However, the effect occurred only with amounts far above the usual therapeutic dose Hirschfelder¹³ stated that caffeine has no

9 Cohn, A. E., and Levine, S. A. The Beneficial Effects of Barium Chloride on Adams-Stokes Disease, *Arch Int Med* **36** 1 (July) 1925

10 Parsonnet, A. E., and Hyman, A. S. Barium Chloride in Stokes-Adams Syndrome of Complete Heart Block, *Am J M Sc* **180** 356, 1930

11 Schwartz, S. P. The Action of Digitalis on Complete Heart Block, *Am Heart J* **4** 408, 1929

12 von Egmond, A. A. J. Ueber die Wirkung einiger Arzneimittel beim vollständigen Herzblock, *Arch f d ges Physiol* **154** 39, 1913

13 Hirschfelder, A. D. Diseases of the Heart and Aorta, ed 3, Philadelphia, J. B. Lippincott Company, 1918, p. 587

effect on the ventricular standstill of clinical heart block In H B , 0.7 Gm of caffeine sodium benzoate was injected intravenously and did not influence the cardiac standstill

Coramin and Metrazol—These substances have actions similar to those of camphor and have been recommended as acute circulatory and respiratory stimulants Both substances have been used with apparent success in resuscitation by intracardiac injection into the asystolic heart As was pointed out by Hyman,¹⁴ it is difficult to determine whether it is the drug or the needle puncture which restores the rhythmic function to the heart In H B , 3 cc of coramin injected intravenously, and on another occasion 2 cc of metrazol, was without effect on the induced cardiac standstill

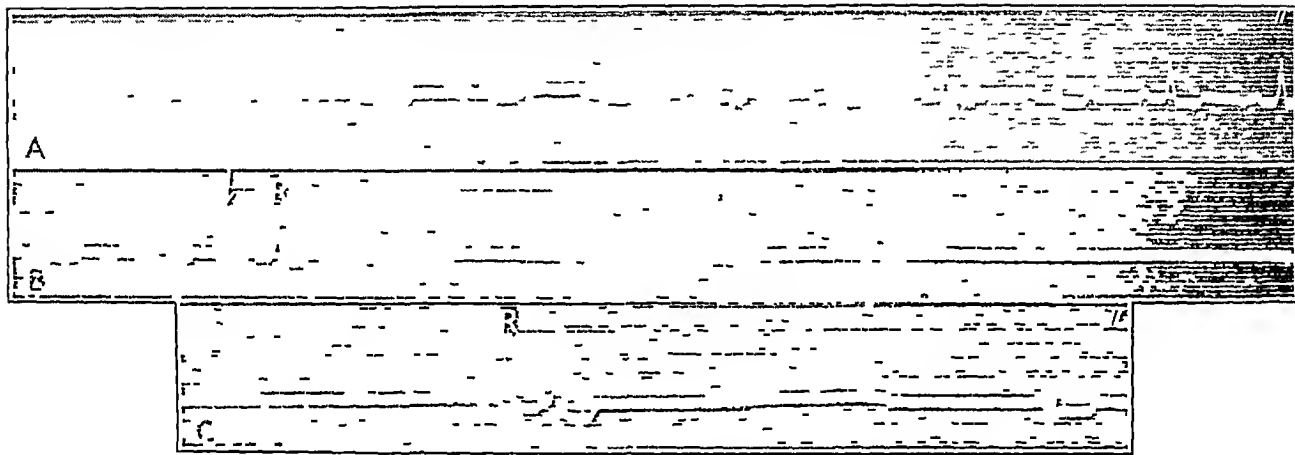


Fig 3 (H B) —B and C show a standstill of ten and eight-tenths seconds At this time the patient had received 15 mg of thyroxine intravenously in divided doses

Thyroxine—That thyroxine increases the irritability of the heart is suggested by the tachycardia of hyperthyroidism It has been demonstrated that thyroxine acts directly on the heart¹⁵ It increases the pulsation of cardiac muscle preparations which are devoid of nerve tissue Thyroxine and thyroid have been used with variable results in clinical heart block Blackford and Willius¹⁶ and Drake¹⁷ reported

14 Hyman, A S Resuscitation of the Stopped Heart by Intracardiac Therapy, Arch Int Med 46 553 (Oct) 1930

15 Markowitz, C, and Yater, W M Response of Explanated Cardiac Muscle to Thyroxine, Am J Physiol 100 162, 1932

16 Blackford, J M, and Willius, F A Chronic Heart Block, Am J M Sc 154 585, 1917

17 Drake, E H A Case of Complete Heart Block with Interesting Reaction to Drugs, Am Heart J 3 560, 1928

clinical improvement, while Aub and Stern¹⁸ found that large doses of thyroid increased the auricular rate but did not influence the ventricular rate. In H. B., 15 mg of crystalline thyroxine was administered intravenously in divided doses over a period of five days. The basal metabolism increased from zero to plus 22. Pressure on the right carotid sinus repeatedly induced a long cardiac standstill (fig. 3).

EPINEPHRINE AND CHEMICALLY RELATED COMPOUNDS

The powerful and consistent action of epinephrine and, to a lesser degree, of ephedrine suggested that the prevention of cardiac standstill may depend on the stimulation of the accelerator nervous mechanism of the heart. It seemed, therefore, of importance to study the effect of other drugs which have a similar type of action. Shortly after the discovery of the chemical structure of epinephrine, the physiologic activity of a number of related compounds was investigated. In 1910 Barger and Dale¹⁹ carried out extensive studies and found that sympathetic stimulation which they termed sympathomimetic action was produced by many epinephrine-like substances and that the intensity of the effect increased as these substances approached the composition of epinephrine itself. In all the investigations the response of the blood pressure in the experimental animal has been used almost exclusively as the index of the comparative activities of these epinephrine-like compounds. The quantitative value of the different groups in the epinephrine molecule has been estimated by this method, and this has formed the basis for the synthesis of additional compounds. It was pointed out by Barger and Dale¹⁹ that a substance showing an epinephrine-like pressor response may not reproduce all the other effects of epinephrine in the same degree. Since there do not appear to be any reports on the relative effects of these compounds on the human heart, a study was carried out by the present method to determine the influence of chemical structure on this particular physiologic action. Aside from theoretical considerations, this seemed to be of some practical importance, since a number of synthetic substances are now marketed as substitutes for epinephrine.

The reaction to natural epinephrine was used as a standard for comparison, and the response to varying doses of epinephrine was first

18 Aub, J. C., and Stern, N. S. The Influence of Thyroid Extract on the Total Metabolism and Heart in a Case of Heart Block, *Arch. Int. Med.* **21**: 130 (Jan.) 1918.

19 Barger, G., and Dale, H. H. Chemical Structure and Sympathomimetic Action of Amines, *J. Physiol.* **41**: 19, 1910.

determined After a control electrocardiogram showing the effect of pressure on the carotid sinus had been made, the drug was administered intravenously, and records were taken after one minute, and then at frequent intervals thereafter until the standstill could again be reproduced The reactions to 0.2, 0.05, 0.02 and 0.01 mg were obtained in this manner The results were a series of electrocardiograms in which the rate of the ectopic pacemaker and the duration of the effect could be determined Repeated injections of these doses at different times revealed a definite consistency in the reactions It was found that the rate of the ectopic pacemaker and the duration of the effect were proportional to the dose

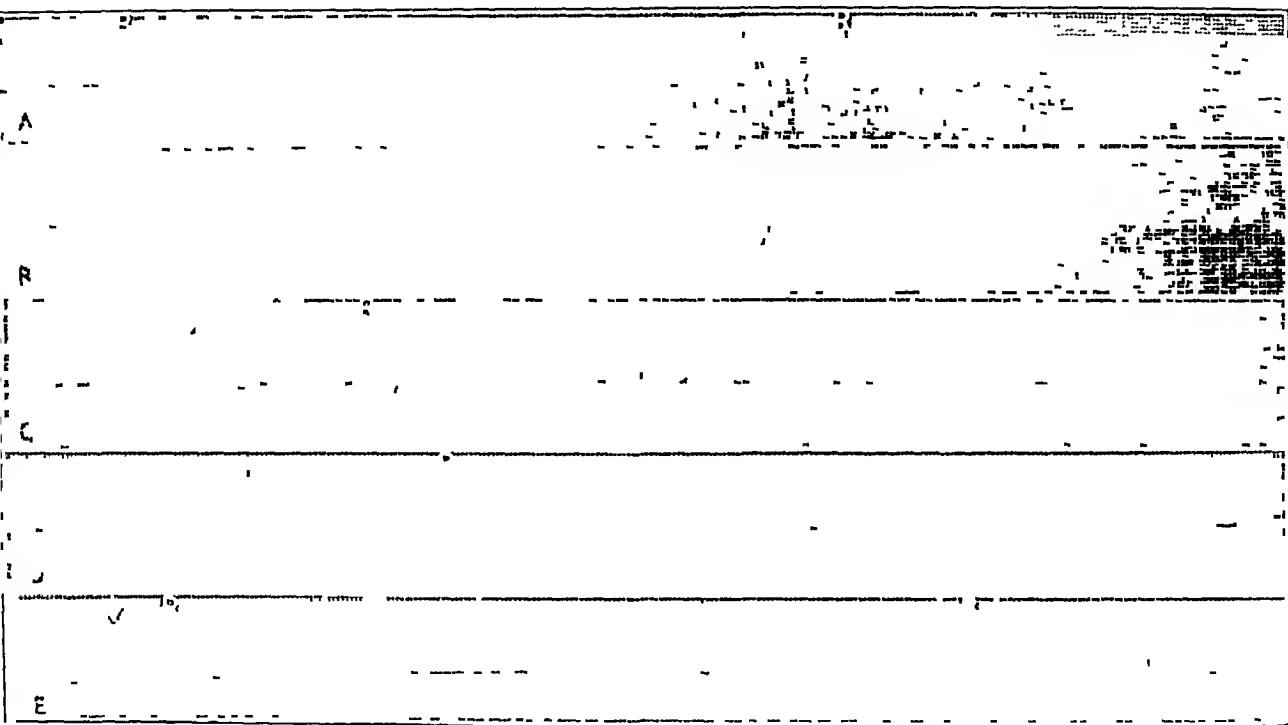


Fig 4 (H. B.)—*A* shows an induced standstill of six seconds *B* shows a maximum rate of 100 with multiple rhythmic foci *C* and *D* were made after the intravenous administration of 0.2 mg of l-epinephrine *E* was made twenty-five minutes after the injection

administered For example, 0.2 mg of epinephrine resulted in a rapid ventricular rhythm from multiple foci, the maximum rate being 100 and the duration twenty-five minutes (fig 4) The smaller doses induced ventricular rhythms from a single focus, the rate and duration varying with the dose (figs 5 and 6) The reactions of the epinephrine-like compounds were studied in the same manner, and the resulting records compared with those obtained with the different doses of epinephrine, thus permitting an estimation of the ratio of activity between epinephrine and the related compounds

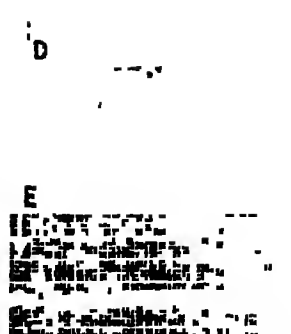


Fig 5 (H B) — *A* shows an induced standstill of seven and six-tenths seconds *B*, taken one minute after the intravenous administration of 0.05 mg of l-epinephrine, shows ventricular rhythm, the rate is 60 *E* shows the disappearance of the effect fifteen minutes after the injection of the drug

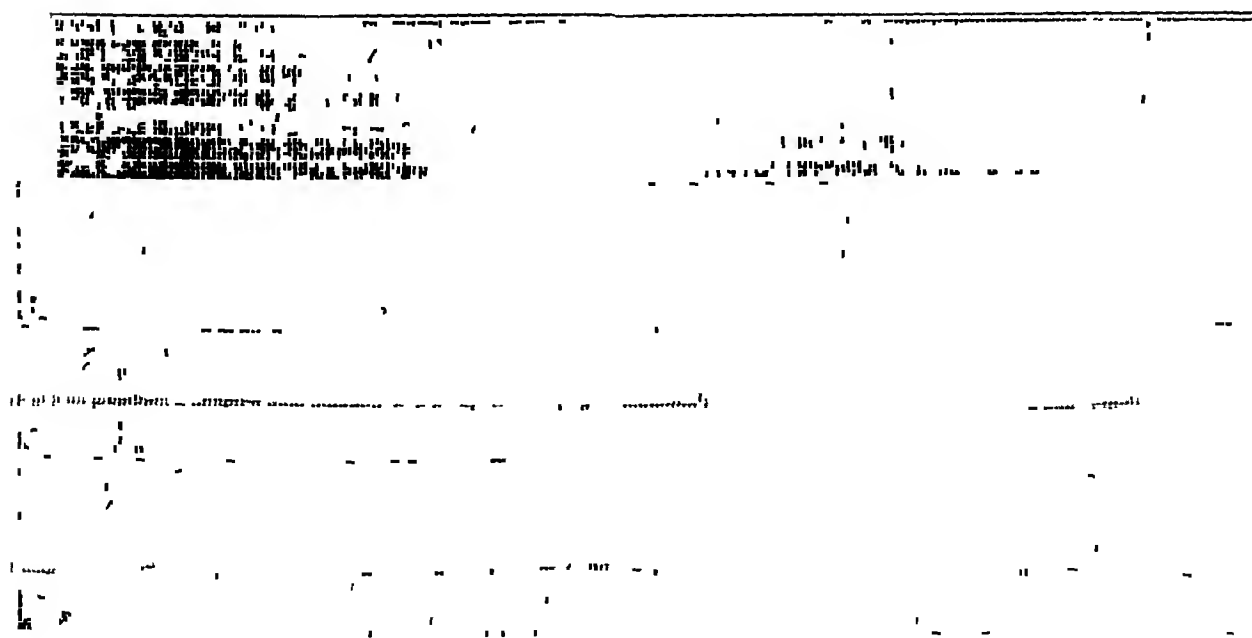
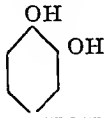
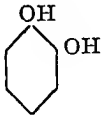


Fig 6 (H B) — *A* shows an induced standstill of five and two-tenths seconds *B*, taken one minute after the intravenous administration of 0.01 mg of l-epinephrine, shows ventricular rhythm, the rate is 33 *D* shows the disappearance of the effect seven minutes after the injection

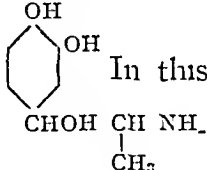
It is not the purpose of the present report to discuss in detail the chemical structure of the various compounds but merely to point out the essential differences from the composition of epinephrine

Epinephrine  is the laevo isomer of an amine consisting of a

catechol nucleus  and a side chain $\text{CHOH CH}_2 \text{NHCH}_3$ containing the amine group. The epinephrine substitutes are either optical or chemical isomers of epinephrine or have some alteration in the structure affecting the nucleus or the side chain or both

Optical Isomers—Natural epinephrine is laevorotatory, while the synthetic base is racemic. In 1908 the dextrocomponent became available for study and practically all agree that the d-isomer has a relatively weaker action. Ratios of activity on the blood pressure in experimental animals varying from 1/12 to 1/40 have been reported.²⁰ According to Tanter²¹ the median figure is 1/20. In H. B., in three experiments 1 mg. of d-epinephrine produced a response practically identical with that obtained by 0.05 mg. of natural epinephrine, thus giving a ratio of 1/20. It is evident therefore that owing to its content of the relatively weak dextrosubstance the synthetic epinephrine is approximately one-half as effective on the heart as natural epinephrine.

Chemical Isomers—The only chemical isomer studied was a synthetic substance, α hydroxy β amino 3, 4 dihydroxy propylbenzene

having the following structural formula  In this compound the

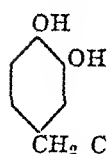
methyl group which in epinephrine is bound to the nitrogen is transferred to the carbon side chain. It is stated that this compound does not produce the effect on the vagus (drop in blood pressure in animals which have not received atropine) and that it is from seven to ten times less toxic than epinephrine. It was necessary to use 0.5 mg. of this

20 Cushny, A. R. The Action of Optical Isomers, *J. Physiol.* **37** 130, 1908, Further Note on Adrenalin Isomers, *ibid.* **38** 259, 1909. Launoy, L., and Menguy, B. Documents numeriques sur les adrenalins, droite, gauche et sur l'adrenalone, *Compt. rend. Soc. de biol.* **87** 1066, 1922. Fromherz, K. Die Blutdruckwirkung des racemischen suprarenins und seiner optisch aktiven Komponenten, *Deutsche med. Wchnschr.* **49** 814, 1923.

21 Tanter, M. L. Comparative Actions of Sympathomimetic Compounds Catechol Derivatives, *J. Pharmacol. & Exper. Therap.* **40** 43, 1930.

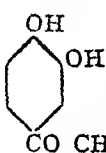
substance to obtain a response comparable to that produced by 0.05 mg of the epinephrine, so that it is approximately one-tenth as active.

Synthetic Substances Resembling Epinephrine—The compound



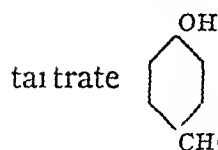
is a synthetic substance closely resembling epinephrine in chemical

structure except for the absence of the hydroxyl group on the first carbon atom of the side chain. It is marketed in a 1 per cent solution as a substitute for epinephrine. Barger and Dale¹⁹ found that the absence of the hydroxyl group in this position greatly reduced the pressor activity. Tainter²¹ observed that the drug was approximately one-twelfth as active on the blood pressure of cats, and Jackson²² reported that this substance was about one-tenth as active on the blood pressure as epinephrine. By the present method it was found that approximately forty times as much of this substance was required to produce a response comparable to that obtained by 1-epinephrine.

The compound  differs from epinephrine only in having a ketone

in place of the hydroxyl group in the side chain. Barger and Dale¹⁹ found that the substitution of a ketone markedly reduced the effect on the blood pressure, and Tainter²¹ observed that approximately from one hundred to two hundred times as much of this drug as of 1-epinephrine was needed to cause the same pressor response in cats. By the present method 8 mg of the substance produced a response on the ventricular rhythm comparable to that obtained by 0.2 mg of 1-epinephrine, indicating a ratio of activity to epinephrine of 1:40 (fig. 7).

Synephrin Tartrate and Neosynephrine Hydrochloride—Synephrin



tartrate is a synthetic amine which differs from epinephrine in

that there is but one hydroxyl on the benzene ring so that the nucleus is a phenol instead of a catechol. The side chain is unchanged. It is more stable and less toxic than epinephrine. In the German literature this compound has been widely recommended as a substitute for epinephrine, the suggested dose being fifty times that of epinephrine. In the application of this substance to induced cardiac standstill, approxi-

²² Jackson, D. E. The Peripheral Action of Certain Drugs, *J. Pharmacol. & Exper. Therap.* 4:291, 1912.

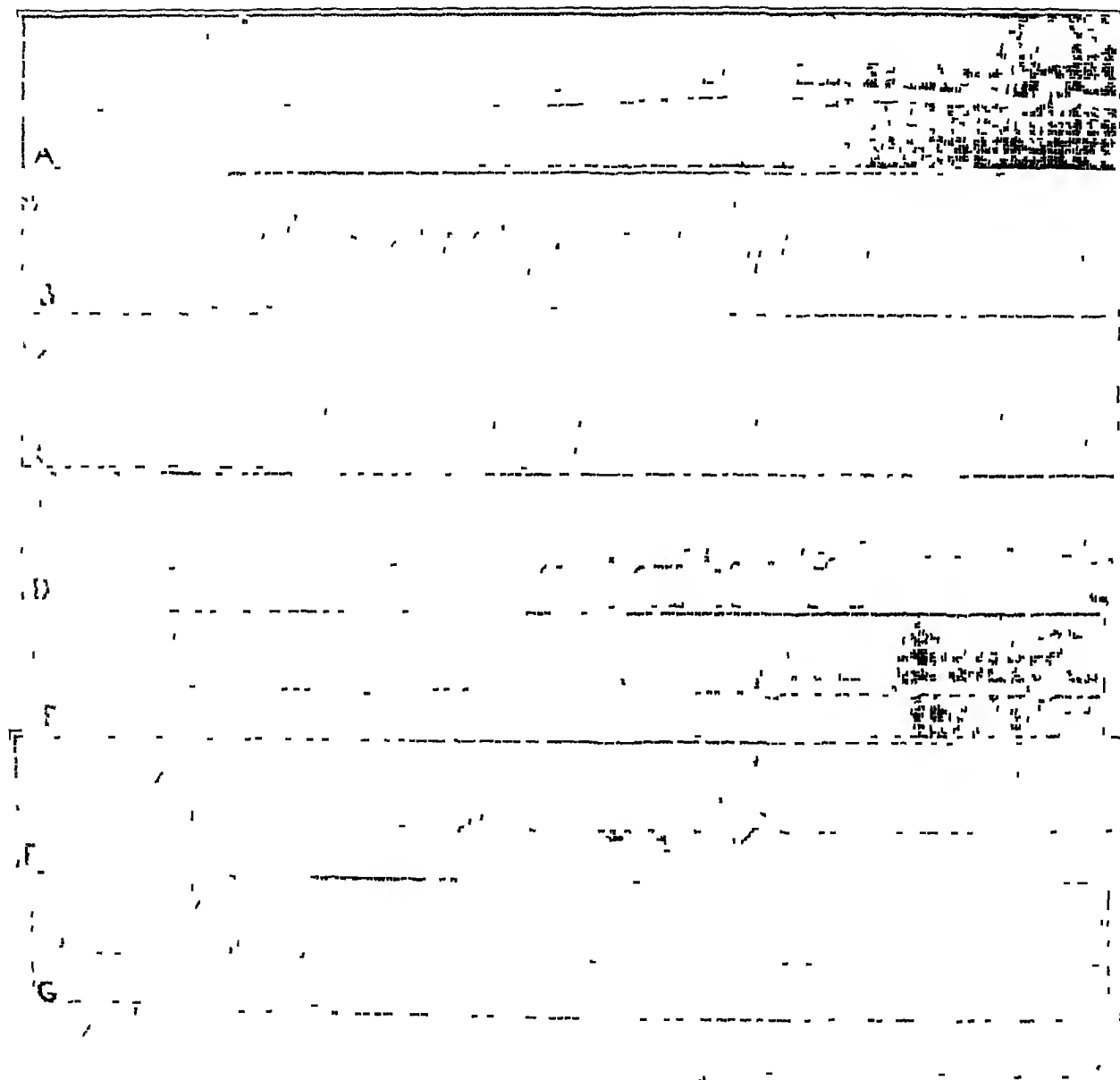
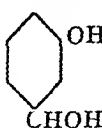



Fig 7 (H B) — *A* shows an induced standstill of eight and two-tenths seconds. The lower tracings were taken after the intravenous administration of 8 mg of a compound differing from epinephrine only in the substitution of a ketone for the hydroxyl group in the side chain. The maximum ventricular rate was 100, one minute after the injection. *H* was made twenty-five minutes after the injection. This response compares with that shown in figure 8.


mately four hundred times as much synephrin tartrate was required to produce the same effect as epinephrine

Neosynephrin hydrochloride  has the same chemical composition

as synephrin tartrate, differing only in that the hydroxyl group on the benzene ring is in the meta instead of the para position. This substance was found to be more active than synephrin tartrate. Two milligrams of neosynephrin hydrochloride, given intravenously, induced a response comparable to that of 0.02 mg of epinephrine, indicating a ratio of 1:100.

Tyramine—Tyramine  differs essentially in chemical structure

from epinephrine in the absence of one hydroxyl group on the nucleus and a hydroxyl on the side chain. Tyramine was found in ergot by Barger and Dale¹⁹ and is now prepared synthetically. The substance is not used in therapy, but Hewlett and Kay²³ showed that in normal men subcutaneous injections of 60 mg produced a prolonged rise of the blood pressure, and they recommended its use in surgical shock. Dale and Dixon²⁴ considered that the action of tyramine was the same as that of epinephrine, differing merely in degree and duration of effect. Tainter,²⁵ however, concluded that the principal action of tyramine was direct muscular stimulation and that sympathetic stimulation was not prominent. By the present method it was found that tyramine produced qualitatively the same reaction on the heart as epinephrine. A response comparable to that evoked by 0.05 mg of epinephrine was produced by 60 mg of tyramine, thus giving a ratio between tyramine and epinephrine of 1:1,200.

Hordenine—Hordenine  is present in the germ of malt


grains and is closely related in structure to tyramine, differing only in having two methyl groups attached to the side chain. Barger and Dale¹⁹ demonstrated that hordenine produced a very weak pressor reac-

23 Hewlett, A. W., and Kay, W. E. The Effect of Tyramine on Circulatory Failure, *J. A. M. A.* **70** 1810 (June 15) 1918.

24 Dale, H. H., and Dixon, W. E. The Action of Pressor Amines Produced by Putrefaction, *J. Physiol.* **39** 25, 1909.

25 Tainter, M. L. The Action of Tyramine on the Circulation and Smooth Muscle, *J. Pharmacol. & Exper. Therap.* **30** 163, 1926.

tion in animals, and Jackson²⁶ observed that this compound was an effective bronchial dilator, but had only a slight pressor action as compared with epinephrine. Sixty milligrams of hordenine sulphate produced a response on the induced cardiac standstill somewhat less intense than that of 0.01 mg of epinephrine, giving a ratio of approximately 1:6,000.

Ephedrine—Ephedrine  differs from epinephrine in chemical structure in the absence of two hydroxyls on the nucleus and in having an additional atom of carbon in the side chain. It has been demonstrated by Barger and Dale²⁷ that both of these changes definitely weaken the pressor activity. Although ephedrine has been the subject of much investigation, it has not been conclusively demonstrated that it reproduces all of the physiologic reactions of epinephrine. Certain observations suggest qualitative differences in the action of the two drugs on the heart. Gradinesco²⁷ found that epinephrine restores the beat of a frog's heart which has been arrested by perfusion with ephedrine. La Barre²⁸ showed that ephedrine did not lead to ventricular fibrillation in cats under chloroform anesthesia, in which respect it differed from epinephrine. The present experiments, however, demonstrate that ephedrine increases cardiac rhythmicity in the same manner as epinephrine, differing only in degree. Chen²⁹ found the ratio of pressor activity of ephedrine to epinephrine to be 1:142. In three subjects it was possible to make a quantitative comparison of epinephrine and ephedrine by the present method. In H. B. 100 mg of ephedrine produced a response comparable in intensity to that of 0.05 mg of epinephrine, giving a ratio of 1:2,000 (fig. 8). The duration of the effect was one hour and forty-five minutes as compared with fifteen minutes for the same amount of epinephrine. It is interesting that Chen and Meek³⁰ found that in dogs for a certain rise in blood pressure the duration of the effect of ephedrine was also seven times greater than that of epinephrine. In two other subjects the approximate ratios were between 1:1,500 and 1:2,000. It is apparent that ephedrine has a

²⁶ Jackson, D. E. The Action of Drugs on Bronchioles, *J. Pharmacol. & Exper. Therap.* **5**: 491, 1914.


²⁷ Gradinesco, A. Difference d'action entre l'éphedrine et l'adrénaline, *Compt. rend. Soc. de biol.* **96**: 1027, 1927.

²⁸ La Barre, J. Existe-t-il une syncope éphédrino-chloroformique, *Compt. rend. Soc. de biol.* **98**: 863, 1928.

²⁹ Chen, K. K. A Comparative Study of Synthetic and Natural Ephedrines, *J. Pharmacol. & Exper. Therap.* **33**: 237, 1928.

³⁰ Chen, K. K., and Meek, W. J. A Comparative Study of Ephedrine, Tyramine and Epinephrine with Special Reference to the Circulation, *J. Pharmacol. & Exper. Therap.* **28**: 59, 1926.

decidedly weaker effect on the cardiac rhythmicity than on the blood pressure as compared with epinephrine. This indicates that for the prevention of cardiac standstill ephedrine must be administered in doses larger than those ordinarily employed to raise the blood pressure.

Phenylethanolamine — Phenylethanolamine  differs essentially

from epinephrine in the absence of two hydroxyls on the nucleus. Alles³¹ has synthesized this compound and studied its physiologic prop-

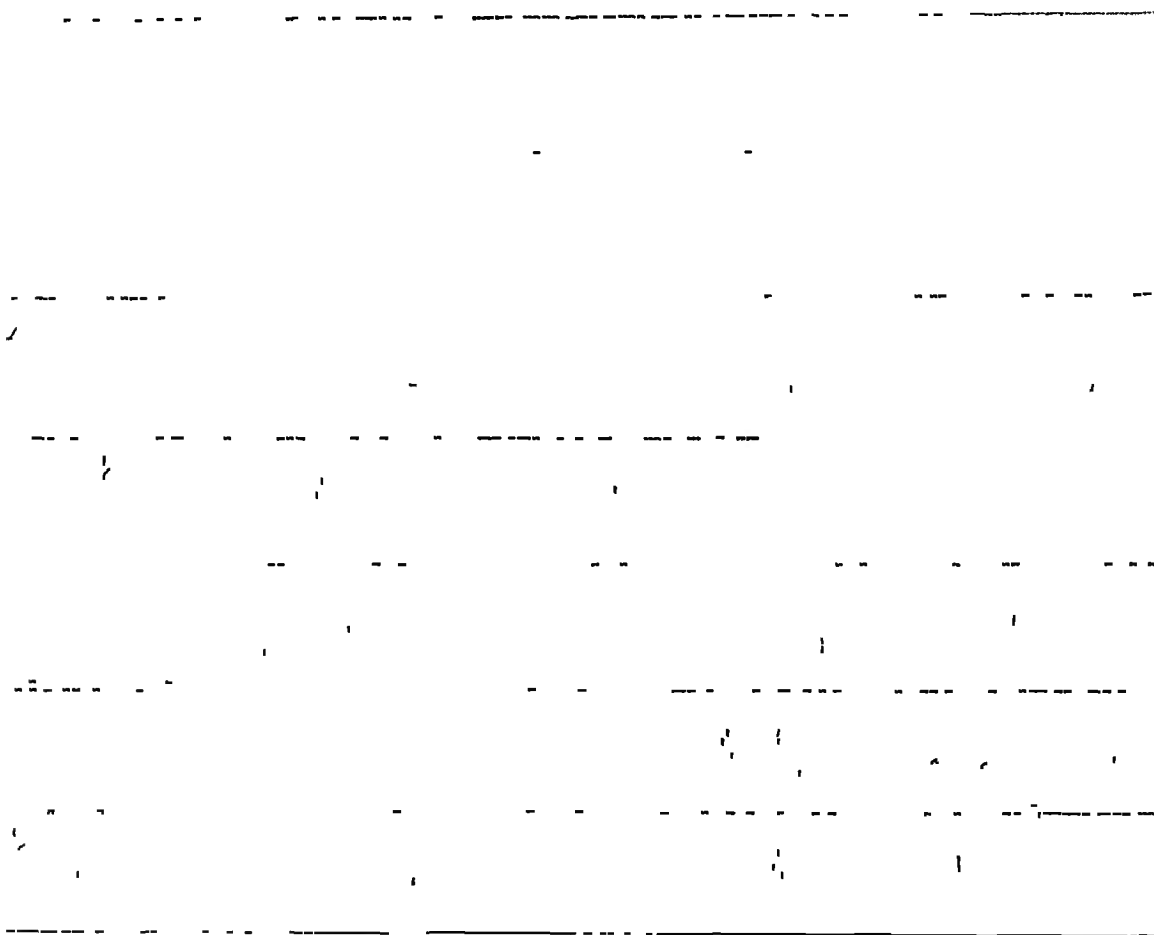


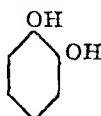
Fig 8 (H B) — *A* shows induced standstill of nine and six-tenths seconds. The lower tracings were made after the administration of 100 mg of ephedrine sulphate intravenously. The maximum rate of ventricular rhythm is 60. This response compares in intensity with that shown in figure 5.

erties and toxicity. It produces an increase in the rate and amplitude of the cardiac contraction with a definite rise in blood pressure. Tainter³² found that phenylethanolamine had actions on the circulation

³¹ Alles, G. A. Comparative Physiological Action of Phenylethanolamine, *J Pharmacol & Exper Therap* **32** 121, 1928.

³² Tainter, M. L. Pharmacological Actions of Phenylethanolamine, *J Pharmacol & Exper Therap* **36** 29, 1929.

similar to that of ephedrine and tyramine. Miller and Piness³³ have used the drug in clinical cases and have observed slight rises in blood pressure following the subcutaneous injections of 100 mg of the substance. In H. B. the injection of 160 mg intravenously produced a reaction comparable to that caused by 0.02 mg of epinephrine, giving a ratio of activity of 1:8,000.

Catechol—Catechol  is the nucleus of the epinephrine mole-

cule, and Dakin³⁴ concluded that catechol was necessary for the production of an action of epinephrine, stating that catechol itself stimulated sympathetic nerve endings in the same manner as epinephrine. Barger and Dale,¹⁹ however, concluded that catechol was an unessential constituent for stimulation of the peripheral sympathetic nerve, and that its action was not related to that of epinephrine. The injection of 200 mg of catechol intravenously was without effect on the induced cardiac standstill, confirming the conclusion of Barger and Dale that this substance does not possess a sympathomimetic action.

COMMENT

Information regarding the effectiveness of drugs on cardiac standstill in man has been derived from two sources: (1) the response of the asystolic heart to various intracardiac injections, and (2) the effect of drugs in the prevention of the Adams-Stokes seizures of heart block. The conclusions from these sources are open to objection since resuscitation by intracardiac injection may be due in part to the mechanical stimulation of the needle puncture. There is also a spontaneous variation in the frequency of the Adams-Stokes seizures of heart block, so that a favorable response cannot safely be attributed to the administered drug. A large variety of compounds unrelated in chemical composition or in physiologic action have been employed, and in many instances favorable results have been reported. This has led to the suggestion that the response of the heart is no specific for any pharmacodynamic action.¹⁴


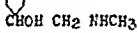
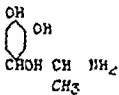
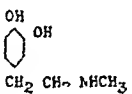
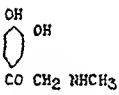
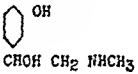
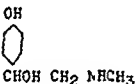
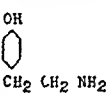
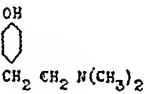
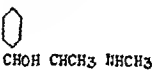
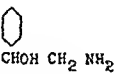

By the present method the action of a drug on cardiac standstill can be observed under controlled conditions and the effectiveness estimated quantitatively. The results indicate that many substances which are used in the prevention and treatment of cardiac standstill are entirely inactive. For example, digitalis is administered as an emergency mea-

³³ Miller, H., and Piness, G. A Synthetic Substitute for Ephedrine, *J. A. M. A.* 92: 1033 (Oct. 6) 1928.

³⁴ Dakin, H. D. On the Physiological Activity of Substances Indirectly Related to Adrenalin, *Proc. Roy. Soc. London, s. B.* 76: 493, 1905.

sure in cardiac arrest such as occurs during a surgical operation. The present observations indicate that a single dose of digitalis cannot stimulate cardiac rhythmicity and is therefore ineffective. Actually this drug may be distinctly harmful, tending to prevent the spontaneous return of the rhythmic function.

Comparative Effects on Cardiac Standstill
of Compounds Related to Epinephrine

Drug	Structural Formula	Approximate Ratio of Activity to 1-epinephrine
1-epinephrine		1 : 1
d-epinephrine		1 : 20
α -hydroxy β -amino 3,4-dihydroxy propyl- benzene		1 : 10
Synthetic Substance		1 : 40
Synthetic Substance		1 : 40
Neosynephrin hydrochloride		1 : 100
Synephrin tartrate		1 : 400
Tyramine		1 : 1,200
Hordenine		1 : 6,000
Ephedrine		1 : 1,500 - 1 : 2,000
Phenylethanolamine		1 : 8,000
Catechol		Ineffective

The compounds were in the following forms: 1-epinephrine, α -hydroxy β -amino 3,4-dihydroxy propylbenzene and the first-mentioned "Synthetic Substance" as hydrochlorides; d-epinephrine as the bitartrate, tyramine and hordenine, ephedrine and phenylethanolamine as the sulphates.

The activity of the various sympathomimetic amines suggests that the response of the heart is the result of a specific pharmacodynamic action, namely, stimulation of the cardiac accelerator mechanism, and only drugs possessing this action are likely to be effective on cardiac standstill.

In the application of the present observations to the therapy of cardiac standstill it is apparent that natural epinephrine is the most

11 Ephedrine and phenylethanolamine in large doses are effective by mouth and are applicable in certain cases of heart block

Dr Arthur D Hirschfelder of the Department of Pharmacology assisted in this work with helpful suggestions

1127 Medical Arts Building

DISCUSSION

DR ARTHUR D HIRSCHFELDER, Minneapolis In this series of observations Dr Nathanson has opened up a new avenue for the study of the properties of the human ventricle which is beating independently and for a quantitative study of the relative activities of various drugs His studies have shown the relations that exist between effects on vasoconstriction and effects on ventricular rhythmicity, and these will certainly be of great practical applicability Few clinical studies, except the classic studies of His and of Erlanger on heart block are comparable to them in thoroughness and in beauty of execution The relative activities of the drugs of the epinephrine and ephedrine series and the relation of the chemical constitution to the actions in clinical cases which Dr Nathanson has presented so closely resemble the observations previously made in experiments on animals (Barger and Dale, Chen, Tainter and others) that they will certainly lead to the development of new standards of comparison and to more certain clinical therapy, which further studies along these lines will probably confirm and render more definite

MORPHOLOGIC VARIETIES OF BRONCHIECTASIS IN THE ADULT

THEIR PROBABLE PATHOGENESIS AND CLINICAL DIFFERENTIATION

RAPHAEL A BENDOVE, MD
AND
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Pathologists have long described various forms of bronchial dilatation, such as cylindric, globular and saccular, but until recently no attempt was made to differentiate these bronchiectatic forms clinically. The introduction of iodized poppy-seed oil 40 per cent as a safe diagnostic means in the roentgenologic exploration of the bronchial tree made it possible to visualize and study the various morphologic types of bronchiectasis in the living and has led to an almost complete revision of the hitherto accepted views on the clinical aspects of the condition. Studies by Bezançon, Weil, Azoulay and Bernard,¹ Reinberg² and others have definitely established the fact that marked bronchiectasis may exist without bronchorrhea or cough, and that the amount of bronchial secretion bears no causative relation to the development of bronchial dilatation. Gauthier,³ Sergent and Jobin⁴ and others have drawn attention to the widely divergent ways in which bronchiectasis may manifest itself and to the variable clinical course which it may pursue. Ballon and Ballon⁵ described a roentgenologic classification of bronchiectasis without, however, correlating the various forms with their clinical features.

The roentgen images of bronchiectasis as outlined with iodized oil are multiform and have been variously described as cylindric, saccular, globular, clubbing, beaded, varicose, fusiform, like a pigeon's nest, a raisin seed or fingers of a glove, etc. Some of the terms could no doubt be used synonymously, and some of the forms when analyzed properly

1 Bezançon, Weil, Azoulay and Bernard. *Forme sèche hémoptoïque de la dilatation des bronches*, *Presse med* **15** 157 (Feb 20) 1922

2 Reinberg, S. A. *Roentgen-Ray Studies on the Physiology and Pathology of the Tracheobronchial Tree*, *Brit J Radiol* **30** 451, 1925

3 Gauthier, G. *Contribution à l'étude de formes larvées de la dilatation des bronches chez l'adulte*, *Thèse de Lyon*, 1925

4 Sergent and Jobin. *Les images radiologiques dans les formes fétides et nonfétides de la dilatation des bronches*, *Bull Acad de méd, Paris* **99** 582 (May 29) 1928

5 Ballon, D. H., and Ballon, H. C. *Pneumonography with Iodized Oil, 40 per Cent, by the Bronchoscope Method*, *Arch Surg* **14** 184 (Jan) 1927

from the pathogenic and clinical point of view would prove to be sub-varieties or evolutive stages of the same type. We have attempted to classify into six definite varieties the numerous cases of bronchiectasis which we observed at the Cumberland Hospital and Clinic, at the Pulmonary Clinic of the Post-Graduate Hospital (Bendove) and in our private practice. The classification includes five morphologic types of bronchiectasis and one of bronchiolectasis, each of which is characterized by a more or less distinctive clinical syndrome and is considered to be the result of different pathogenic factors both structural and functional. In a previous contribution,⁶ we discussed fully the physiopathologic changes which may precede or accompany the ectatic condition of the bronchus, and we indicated the diagnostic significance of these impaired functions in the early stages of the several forms of bronchiectasis. Before describing the morphologic appearance of each bronchiectatic variety, we find it pertinent to review briefly the recent contributions on the respiratory and expulsive functions of the bronchi which have thrown new light on the pathogenesis of bronchiectasis in general.

PATHOLOGIC PHYSIOLOGY OF ECTATIC BRONCHI

Studies by Reinberg,² Macklin,⁷ Miller,⁸ Bullowa and Gottlieb⁹ and others have yielded many new facts regarding the respiratory dynamics of the bronchi and their elaborate protective or expulsive mechanism. The physiologically functioning bronchi are not merely conducting tubes for distributing air to, and collecting it from, the alveoli but are actively participating in the process of pulmonary inflation and deflation. The respiratory movements of the bronchi consist of an inspiratory elongation with widening of the caliber and an expiratory shortening with constriction of the caliber. The structure of the bronchial wall is admirably adapted to these rhythmic changes in length and width, which are synchronous with the respiratory phases (Miller and Macklin). Pathologic processes which involve the fibro-elastic or myo-elastic layers of the bronchus render it more or less stiff and hinder its respiratory function. Rigid bronchi of this sort can be studied clinically by intra-bronchial instillation of radiopaque substances, and Bonnamour, Badolle

6 Bendove R. A. and Gershwin B. S. The Inverse Ratio in the Roentgenologic Visualization of the Bronchi and Alveoli After the Injection of Contrast Media, *Am. J. Roentgenol.* **31** 323 (March) 1934.

7 Macklin C. C. The Musculature of the Bronchi and Lungs, *Physiol. Rev.* **9** 1 (Jan.) 1929.

8 Miller W. S. Key Points in Lung Structures, *Radiology* **4** 173, 1925, Musculature of Bronchial Tree and Its Relation to Certain Pathologic Conditions, *Am. Rev. Tuberc.* **5** 689, 1921.

9 Bullowa, J., and Gottlieb, C. Experimental Studies in Bronchial Function, *Laryngoscope* **32** 284 (April) 1922.

and Gaillard¹⁰ described this phenomenon as the "lipiodoladiologic syndrome of bronchial immobilization" which is present in cases of chronic bronchitis and early bronchiectasis (figs 1 *A* and 5 *B*)

The involvement of the myo-elastic layers of the bronchus results not only in diminution of its respiratory function but also in the decrease of its evacuative capacity, though the latter depends on other factors as well. The bronchi are endowed with an efficient threefold expulsive mechanism: the cough reflex, the action of the cilia and a progressive wavelike motion said to resemble peristalsis. The cough reflex, according to Reinberg and others, functions best in the trachea and primary bronchus, diminishes in intensity in the secondary and tertiary bronchi

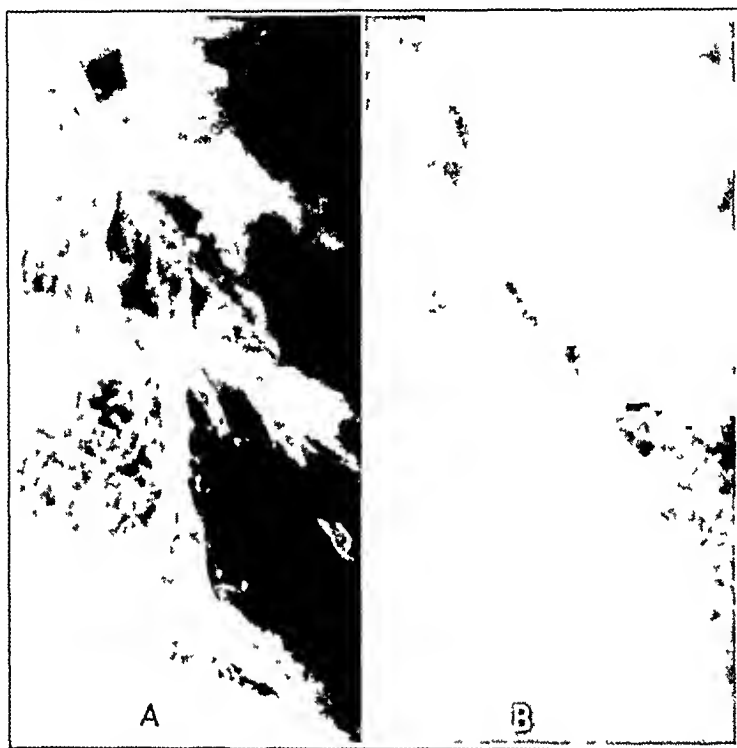


Fig 1—*A*, tubular type of bronchiectasis, the walls of the bronchi are lined with iodized oil, but the lumen is empty, giving the bronchi an appearance of hollow or "macaroni" tubes. *B*, a fusiform subvariety of the tubular dilatation in the inner zone of the lower lobe.

and is absent in the rest of the bronchial tree as well as in the pulmonary parenchyma. Hence, even an extensive peripheral lesion may not cause cough until the inflammatory exudate reaches the bronchi of the first and second order. The cilia which line the entire airway as far as the terminal bronchioles are able to waft up only small irritating particles, and their action becomes easily attenuated by a catarrhal condition. The peristaltic movements were studied experimentally by Reinberg² and

10 Bonnamour, S., Badolle, A., and Gaillard, R. *Le radio-diagnostic dans les affections broncho-pulmonaires par le lipiodol*, Paris, L'expansion scientifique française, 1929.

Hudson and Hane¹¹ and were found to be present in the entire tract, including even the airway terminals. This expulsive phenomenon is dependent mostly on the bronchial musculature, though the integrity of the mucosa and the sensory nerve endings found therein is also essential for the proper reflex stimulation. Pathologic involvement of any of these bronchial coats will result in a lessening of the evacuative capacity of the bronchus in question, the degree of functional diminution bearing a relation to the extent and type of lesion and the particular bronchial layer thus affected.

Our observation, which was fully described in a previous contribution,⁶ that a physiologically functioning bronchus rids itself of the injected iodized oil in about twenty minutes, is in accord with that of Bonnamour, Badolle and Gaillard.¹⁰ A bronchus which remains filled with the instilled oil at the end of that period is to be considered a retentive bronchus, the walls of which are either structurally changed or physiologically insufficient. The functional impairment of the bronchus will manifest itself before true ectasia can be detected and the diagnostic significance of this functional test in early bronchial involvement deserves further study. A definitely ectatic bronchus, irrespective of its location, shows a great tolerance toward the injected substances and in certain morphologic types the iodized oil can be found in the bronchus days or even weeks after the injection.

MORPHOLOGIC CLASSIFICATION OF BRONCHIECTASIS AND THE PROBABLE PATHOGENESIS OF EACH TYPE

It must always be kept in mind that ectasia proper is only one manifestation of the multifarious pathologic changes which are brought about in the layers of the bronchial wall by different etiologic factors. The pathologic process may start primarily in the mucosa of the bronchi or in the muscular and elastic layers, or it may originate in the pulmonary parenchyma, implicating the bronchial coats subsequently. These mural changes may be inflammatory, degenerative, sclerotic or suppurative and may involve one or more bronchi at the same time. All of the various pathogenic factors, singly or jointly, determine the resultant ectatic configuration, which can be clearly visualized *in vivo* by means of intrabronchial injection of a contrast medium such as iodized oil.

We differentiated six morphologic types of bronchial dilatation five of which are bronchiectasis and one of which is bronchiolectasis. They are the tubular, cylindric, varicose and globular types, bronchiolectasis and bronchiectatic abscess.

¹¹ Hudson, W. A., and Hane, H. A. Camera Studies of the Tracheobronchial Tree, *Arch. Surg.* **19** 1236 (Dec.) 1929.

Tubular Bronchiectasis—When the dilated bronchi of the tubular form are outlined with iodized oil, they appear like hollow cylinders or tubes, i. e., the walls of the bronchi are lined with the injected material, while the lumen remains empty (fig 1 A). The bronchial mucosa is always involved in this type of ectasia, and the injected material adheres to the diseased membrane, imparting to the bronchi the appearance of empty tubes or "macaroni tubes" (Rosenthal). Catarrhal or inflammatory conditions of the mucosa are, as a rule, the starting pathologic process, with involvement of the other bronchial coats and resultant ectasia. The mucosa of several bronchi may be affected, and the diminution of functional capacity depends on the degree of involvement of the other bronchial coats. The dilatation is, as a rule, uniform in diameter, but a localized constriction in any part of the bronchi caused by accumulated secretion may give rise to fusiform or conical subvarieties of tubular bronchiectasis (fig 1 B). Many French clinicians have stated that this form of bronchial dilatation is always encountered in soldiers who were gassed in the World War, they call it "bronchial dilatation of the gassed" (Bonnamour, Badolle and Gaillard). However, continuous irritation of the bronchial mucosa is likely to give rise to this form of bronchiectasis, and it often follows repeated attacks of bronchitis. Laennec's¹² theory that bronchiectasis is always caused by stagnant bronchial secretions would fit this type of ectasia well, but it would in no way explain the mechanism of production of other forms of bronchial dilatation in which bronchorrhea is absent.

Cylindric Bronchiectasis—A common type of bronchial dilatation is the cylindric form (fig 2 A). When the ectatic bronchi are filled with iodized oil, they look like solid cylinders extending sometimes as far as the periphery of the lung but usually terminating abruptly in any portion of the lobe. As a rule, little alveolar tissue is outlined in the corresponding territory, and the bronchi which are filled with the iodized oil resemble the dry, leafless branches of a tree in winter. The morbidly dilated bronchi have lost much of their resilience as a result of degenerative and sclerotic changes in the myo-elastic layers. The analogous anatomic arrangement of the bronchial and arterial systems has been mentioned by many, and the factors which render the arterial wall vulnerable to sclerosis are no doubt responsible for the sclerotic changes of the bronchial walls, which eventually yield to the constant intrabronchial strain and stress and become permanently and uniformly dilated. Stokes'¹³ description of paralysis of the circular muscle and

12 Laennec, R. T. H. *Traité de l'auscultation médiate et des maladies des poumons et du cœur*, Paris, J. A. Brosson & J. S. Chaude, 1819.

13 Stokes, W. *Treatise on Diagnosis and Treatment of Diseases of the Chest*. Part I. Disease of the Larynx and the Windpipe, Dublin, Hodges and Smith, 1837.

loss of contractility of the bronchi and Andral's¹⁴ suggestion that the nutritional changes in the bronchial wall may precede bronchiectasis could be applied to this type of dilatation

Many subvarieties of the cylindric type of bronchiectasis are encountered—aneurysmal-like pouching, tapering of the distal or proximal end or of both ends of the same bronchus, medial constriction of the bronchial lumen and other morphologic mutations engendered by local inflammatory conditions and mechanical forces. Figure 2 *B* shows a general cylindric type of bronchiectasis of the left lower lobe, one bronchus of which appears markedly dilated, with extreme narrowing of the distal

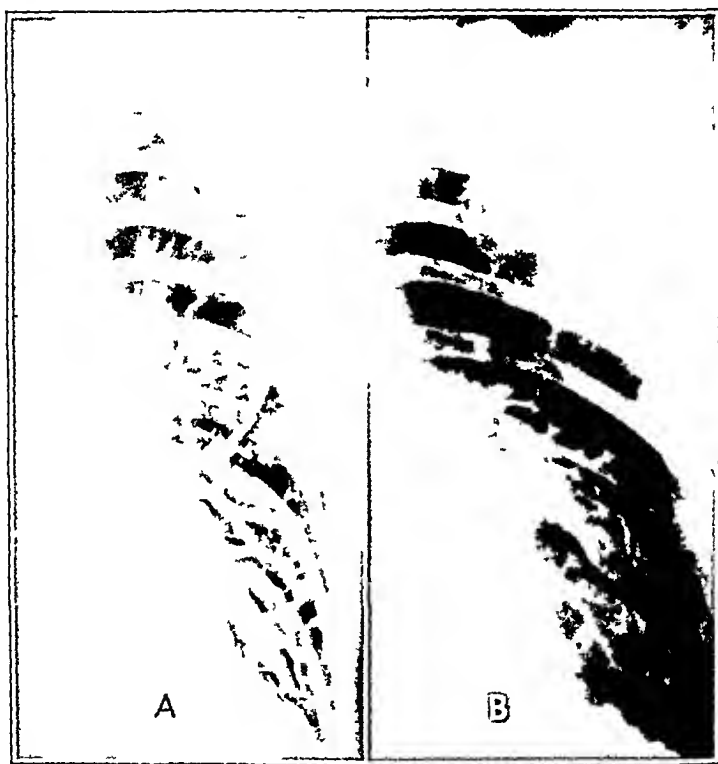


Fig 2—*A*, cylindric form of bronchiectasis, note that the ectatic bronchi, filled with iodized oil, appear like solid cylinders extending in various directions. *B*, conical subvariety of cylindric dilatation with tapering toward the distal end, this type is easily drained

end, which gives it a conical appearance. Drainage is, as a rule, facilitated in this type of ectasia, but when constriction occurs at the middle or proximal end of the bronchus, drainage is much hindered. However, it should be stressed that the cylindric dilatation per se does not cause bronchorrhea, unless secondary inflammatory conditions set in.

Variouse Bronchiectasis—Certain ectatic bronchi into which injections of iodized oil have been made look like swollen, knotted and tortu-

¹⁴ Andral. *Medical Clinic*, translated by D. Spillan, Philadelphia, E. Barington & G. D. Haswell, 1843

ous cords which sometimes stretch from the trachea to the smaller bronchioles (fig 3 *A*) This type of bronchiectasis is always found in cases of pulmonary fibrosis, and the distortion of the bronchi is no doubt due to the irregular traction on the bronchial wall by the cicatrizing parenchyma The pathogenesis of this type of bronchiectasis is in accord with the theory advanced about a century ago by Corrigan,¹⁵ that cirrhosis of the lung is responsible for the dilatation of the bronchi It is obvious that this theory cannot be applied to all other types of bronchiectasis which show only a nominal or no pulmonary fibrosis However, in cases of pulmonary cirrhosis, irrespective of the cause, it is plausible to consider the contraction of the cirrhotic parenchyma as the dominant factor in producing distortion and dilatation of the bron-

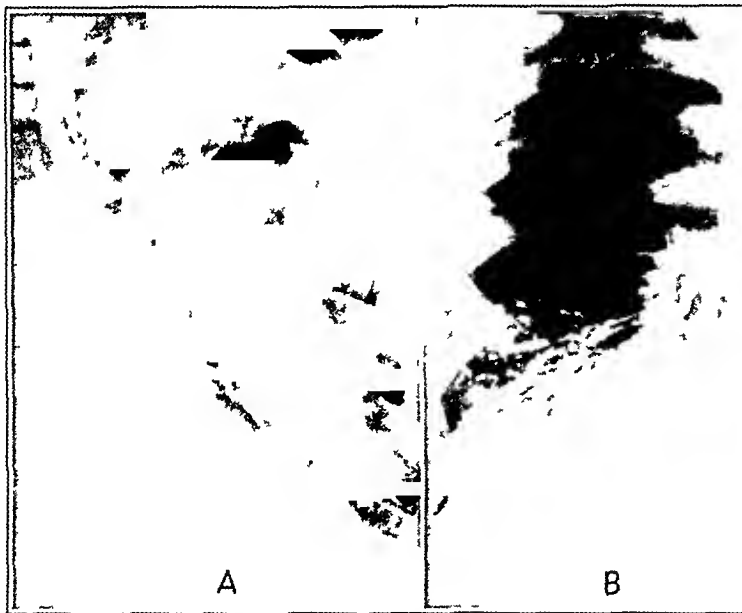


Fig 3—*A* varicose type of bronchiectasis, the bronchi, filled with iodized oil, look like knotted and tortuous cords The trachea, deviated to the left, is also outlined *B*, bronchiolectasis, note the ectatic bronchioles filled with iodized oil, the bronchi appear to retain their normal caliber Both of these forms of ectasia are the result of pulmonary fibrosis

chi in its corresponding territory This form is encountered in pulmonary tuberculosis, atelectasis, pleuritic adhesions, pneumonitis and similar conditions

Bronchiolectasis—Pathogenetically, bronchiolectasis belongs to the type of varicose bronchiectasis, i e, it results from pulmonary fibrosis and atelectasis, but because of its different topographic distribution and morphologic aspect as well as clinical features it is considered to be in a class by itself The dilated bronchioles filled with iodized oil are clustered around the empty bronchi, which seem to retain their normal

15 Corrigan, D Dublin J M Sc 13 266, 1838

anatomic width (fig 4 B) Sometimes the bronchi are not outlined by the injected contrast medium, and only the ectatic bronchioles are visualized. Influenza, bronchopneumonia or other pulmonary lesions of bronchial distribution are the precursors of bronchiolectasis. The diffused fibrosis and atelectasis around the terminal bronchioles produce a dilatation of the bronchioles which may be unilobular, unilateral or bilateral.

Globular or Ampullar Bronchiectasis—In a relatively small number of cases, the iodized oil reveals minute globules or capsules filled with fluid scattered throughout the area into which the injection had been made or suspended from the bronchial stem and resembling a bunch of grapes or scattered raisin seeds (fig 5 A). Many French clinicians are

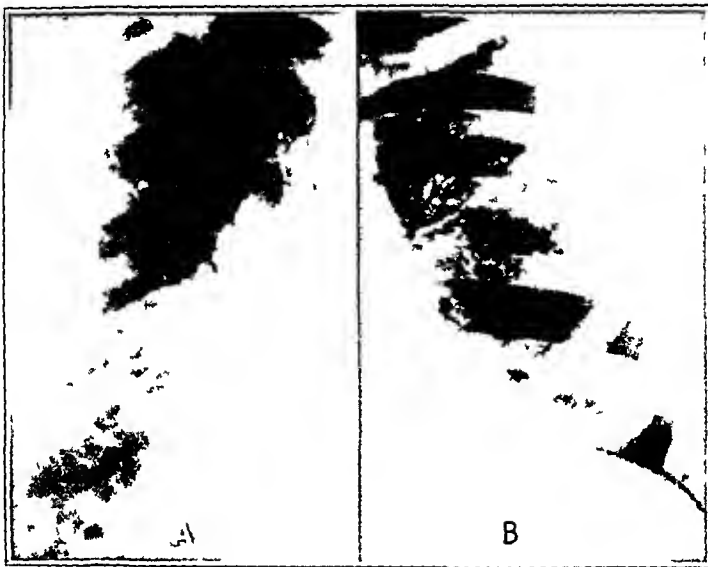


Fig 4—A, globular or ampullar type of bronchiectasis. Note the numerous globules or capsules, partially or completely filled with iodized oil, scattered throughout the pulmonic field like raisin seeds. B, two ectatic segments outlined with iodized oil protrude from the bronchial wall like two cups filled with fluid.

of the opinion that this type of bronchiectasis is usually of syphilitic origin, and they recommend antisyphilitic treatment, even if the Wassermann reaction is negative. It is possible that syphilitic lesions of the bronchi are a frequent factor in the production of this form of ectasia. However, bronchial ulcers of another pathogenesis cannot be excluded. Localized abrasion of the bronchial mucosa may lead to an ulcerative process which gradually penetrates the other layers of the bronchial wall at that point, causing the wall to yield to the constant respiratory stress; the result is localized swelling or segmental dilatation. Figure 5 B shows two apparently recent ulcers filled with iodized oil which protrude from the bronchial wall like two cups filled with fluid. The only symptom complained of by this patient was recurrent slight

hemoptysis which lasted a few minutes and which could be explained by the repeated penetration of the ulcers into a small blood vessel or capillaries. This would correspond to the syndrome described by Bezançon and others in their discussion of dry hemoptotic bronchiectasis, characterized by the "existence of small capsules often grouped in pairs or threes, which show a level line of the injected" iodized oil.

Primary Bronchiectatic Abscess—The cavity of a bronchiectatic abscess may assume any shape or form, it may be multilocular and is usually visualized on the roentgenogram without the use of contrast mediums. Lilienthal¹⁶ expressed the opinion that it usually follows operations for the removal of tonsils and adenoids. Figure 5 A shows

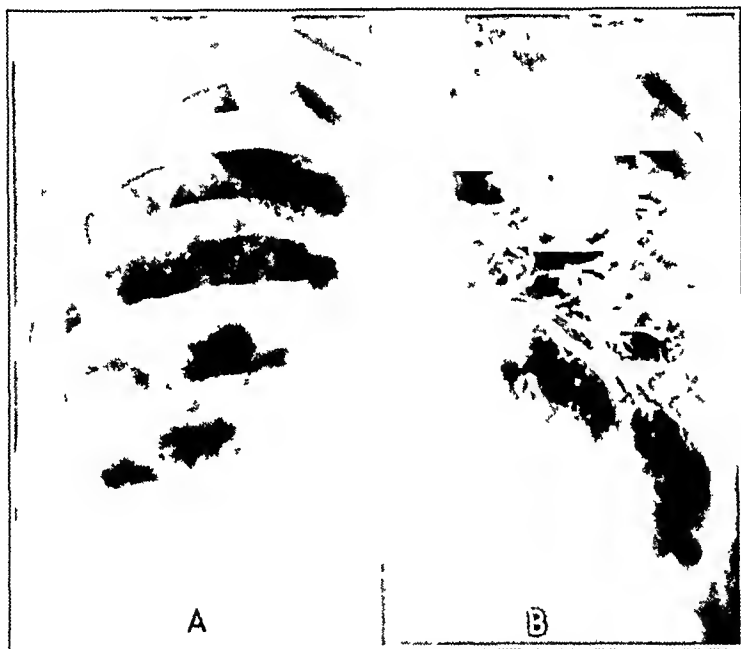


Fig 5—A, multiple bronchiectatic abscess in the right lower lobe. B, an irregular bronchiectatic cavity filled with iodized oil in the left lower lobe, note also the "immobilized" bronchi of normal caliber in the upper lobe retaining the injected oil.

many irregular shadows in the lower pulmonic field which were disclosed by postmortem exploration to be bronchiectatic cavities filled with pus and linked together by intercommunicating bronchial cavities. When the suppuration is preponderantly in the parenchyma, it may cast a homogeneous shadow on the roentgenogram which conceals the underlying bronchial excavation, and only by means of iodized oil is one able to delineate the extent of a bronchiectatic cavity of this nature (fig 5 B).

It should be strongly emphasized that any morphologic type of bronchiectasis may become suppurative, but that the suppuration is

¹⁶ Lilienthal, H. Thoracic Surgery, Philadelphia, W. B. Saunders Company, 1925.

always a late complication evoked by the invasion of pyogenic organisms, aerobic or anaerobic, into the diseased and ectatic bronchi. The clinical course of infected bronchiectasis of this sort may then simulate that of a primary bronchiectatic abscess and may even present all of the grave sequences and sequelae. However, if no secondary infection has taken place, each morphologic type of bronchial dilatation exhibits a more or less distinctive clinical syndrome which is of diagnostic significance in early cases.

We have not included in this classification the bronchiectasis which may follow stenosis of the bronchi caused by extrabronchial pressure, as from aneurysm or mediastinal neoplasm, or by new growth of the bronchial wall. The clinical picture in cases of this sort is usually dominated by the primary lesion, and the bronchiectasis is only a complicating feature. Neither have we included in this classification the congenital types of bronchiectasis which are frequently found in children and have been fully described by pediatricians in this country and abroad. They form a category by themselves.

CLINICAL CONSIDERATIONS

The diverse modes of onset and the variable clinical course of bronchiectasis have been grouped by Gauthier³ into the following clinical forms: the pseudobronchial, the pseudotuberculous, the dry form of Bezançon and the idiopathic form of Baird, to these he adds what he calls the "laeal" forms of bronchial dilatation, which have no characteristic semeiology and which are revealed only by roentgen rays and iodized oil. This clinical classification is a useful attempt at systematizing the various ways in which bronchiectasis may divulge itself but it does not take into account the factors which bring about these clinical variations. Bonnamour, Badolle and Gaillard discussed the close association between the etiologic factors, the morphologic appearance and the clinical varieties of bronchiectasis. They described the ampullar, hollow cylindric and solid cylindric types, the first two types they considered to be distinct clinical entities and in the third type they included all kinds of cylindric dilatation which, they claimed, cannot as yet be differentiated. We find that each of the six morphologic types described previously has its corresponding clinical syndrome, which if not pathognomonic is always indicative of the ectatic condition.

The tubular type of bronchiectasis is revealed primarily through the bronchorrhea. The cough is usually moderate but continuous, and the mucoid or mucopurulent secretion is expectorated with ease and always in small quantities. The sputum is never purulent or foul-smelling. Paroxysmal coughing on lying down is sometimes complained of, this is probably occasioned by the trickling down of secretion from the nasopharynx into the tracheobronchial tree. A history of repeated nasopharyngeal catarrh, of prolonged exposure to inorganic dust and

irritating substances or of being gassed in the World War is of diagnostic importance. Constitutional disturbances rarely occur. Physical signs are of diagnostic value rather by their absence than by their presence, rhonchi may be scattered throughout the chest. The ordinary roentgen plate shows no distinctive pathologic condition. Bronchography is as yet the most important diagnostic criterion of this type of bronchial dilatation.

The clinical syndrome of the cylindric type of bronchial dilatation varies with its distribution and particularly with the evolutive stages of the ectasia. The patient is unable to recollect a striking feature of the onset, which is as a rule insidious. Dyspnea is one of the early symptoms, increasing in intensity with the further augmentation of the bronchiectatic condition. Cough may be absent in the early stages, but it is a distressing symptom in the late stages, when the ectatic bronchi become the seat of bacterial invasion. The cough is usually fitful, being most tumultuous in the morning when the expectoration is most abundant. The physiologically weakened bronchiectatic cavity is tolerant to the secretion, which accumulates gradually until the level of a healthy bronchial region is reached and an evacuative cough is initiated. Sometimes a sudden change in position will induce a fit of coughing which may be explained by the sudden spilling over of secretion from an anasthetic bronchial area into a sensitive bronchial region in which a cough reflex is easily elicited. The sputum may be purulent, in the fusiform subvariety of ectasia sputum is expectorated with great difficulty. In cases of this sort the drainage is poor, and the retained sputum frequently becomes obnoxiously fetid. The retention of sputum may cause fever for a few days, but this will subside after drainage is established. Sometimes the sputum is blood-tinged, and it may be the most significant complaint in early cases of cylindric dilatation, even before catarrhal or suppurative changes have occurred in the bronchial wall. Clubbed fingers are invariably present in the late stages. Physical signs are not typical, there may be dulness on percussion over the ectatic areas when they are filled with secretion, the breath sounds are somewhat altered, and crepitant râles are numerous over and around the ectatic lesion. Cavernous breath sounds may be elicited, particularly in the fusiform and saccular subvarieties. In the early stages of cylindric dilatation adventitious signs may not be elicited. The exact topography and the morphologic subvariety are not revealed by ordinary roentgenology.

The symptoms of the varicose type of bronchiectasis are usually submerged under those of the concomitant pulmonary disease which antedates the ectasia. There is pulling in all directions by scar tissue around the bronchus, which distorts the shape and interferes with the evacuative capacity of the bronchus. Suppurative changes taking place in a bronchus of this nature may stimulate bronchiectasis of the suppurative cylindric type or a bronchiectatic abscess. Pain, which is rather a

are symptom in all other varieties of bronchiectasis, may be complained of in the varicose type as well as in bronchiolectasis. The physical signs are dominantly those of the associated pulmonary lesion, which is as a rule unilateral. Roentgenograms disclose pulmonary involvement, fibrosis and a retraction of the mediastinal structures to the affected side.

The foreground of the clinical picture and the bulk of the physical signs in bronchiolectasis are composed mostly of the pulmonary involvement, which, as a rule, ushers in the condition. A bronchopneumonic disease which, irrespective of its causative agent, lasts for a long time should be suspected of being bronchiolectasis. The cough is, as a rule, hacking, and the expectoration is scanty, usually consisting of tiny rounded masses of sputum. Shortness of breath is noticed, and vague pains in the chest are a frequent complaint. The physical signs are inconclusive, though the character of the râles is more or less distinctive, no râles are heard on ordinary inspiration, but showers of fine râles are elicited over scattered areas of the chest after cough. Roentgenograms may show little deviation from the normal pulmonary roentgenogram.

The globular type of bronchiectasis may betray itself clinically by a sudden severe hemoptysis. It may produce no other recognizable clinical signs, or if infection develops in the diseased bronchial area it may simulate another type of bronchiectatic dilatation. Small hemoptyses may recur frequently. The general condition of the patient is usually well preserved. Neither physical signs nor roentgenologic findings are of diagnostic aid in this type of ectasia. Ectasia of this sort can be individualized only by means of bronchography.

The symptom complex of the bronchiectatic abscess may resemble that of an acute pulmonary abscess or pursue a subacute course with fever, general malaise, lassitude, anorexia, loss of weight and other symptoms. Physical signs change with the vacuity or fulness of the cavity. Roentgenograms reveal single or multiform dense shadows of irregular shapes, sometimes an ill defined cavity may be outlined, particularly if the roentgenogram is taken immediately after drainage, which is rarely complete.

It is often difficult to differentiate between a primary bronchiectatic abscess and other types of bronchial dilatation on which suppurative changes have supervened, but a careful analysis of all clinical antecedents and delineation of the affected bronchi with a contrast medium will greatly facilitate the diagnosis.

The extent of the lesion can never be judged from semeiology alone. Even a large cavity may lack most, if not all, of the signs of cavitation mentioned in the standard textbook. One of us (Bendove¹⁷) discussed fully the mechanism and diagnosis of silent cavities of this sort which may be either absolutely mute, betraying no signs whatsoever, or rela-

tively silent, yielding none of the classic cavernous findings but manifesting other adventitious signs. The early cylindric and globular types are, as a rule, absolutely mute to physical examination, whereas all of the other types are relatively silent, with variable auscultatory signs according to the emptiness or fulness of the cavity, the resilience of the bronchiectatic wall, the uniformity of the caliber and the condition of the surrounding pulmonary tissue.

It should be emphasized that no diagnosis of bronchiectasis is complete unless the location, the distribution and, above all, the type, have been determined, for on this information often depends the therapeutic procedure to be followed. Thus we find that the therapeutic injection of iodized oil is useful in the tubular and early cylindric types, though in the latter iodine medication by mouth or hypodermically is also effective, particularly in combination with a bismuth preparation. In all other forms of bronchiectasis, iodized oil is of doubtful therapeutic value. Ochsner¹⁸ treated a large group of patients with repeated therapeutic injections of iodized oil and found in about 32 per cent complete relief of all symptoms, but he did not state which type of bronchiectasis responded best. Statistical data on the results of treatment in bronchiectasis have little value if the type of the ectasia is not taken into consideration, for unequal elements may thus be compared.

Postural drainage is easily accomplished in the cylindric type, particularly if the dilatation is in the larger bronchi, but it is difficult to evacuate the fusiform and sacculated subvarieties by this means alone and it is altogether insufficient in the varicose type and the bronchiectatic abscess. In these conditions bronchoscopic drainage is essential. It should be stressed that drainage in itself never cures the ectasia irrespective of its form, it affords only symptomatic relief. Intrabronchial treatment in conjunction with intravenous antisiphilitic treatment in cases of the globular type of bronchiectasis deserves clinical trial.

Artificial pneumothorax is effective only in cases of bronchiolectasis which yields even to a low tension compression. If the lesion is limited to one lobe, a selective type of pneumothorax which entails little discomfort to the patient¹⁹ can be created. However, the therapeutic value of artificial pneumothorax is questionable in cases of cylindric or varicose bronchiectasis, as the rigid area will not yield to a collapse of a

17 Bendove, R. A. Silent Pulmonary Cavities. Their Probable Mechanism, Diagnosis and Prognosis, *J. A. M. A.* **87** 1739 (Nov. 20) 1926, *Roentgenology as an Investigational Field in the Mechanism of Physical Signs of the Chest*, *Am. J. M. Sc.* **173** 322, 1927.

18 Ochsner, A. Use of Iodized Oil in the Treatment of Bronchiectasis, *S. Clin. North America* **10** 843, 1930.

19 Bendove, R. A. Selective Therapeutic Pneumothorax in Acute Pulmonary Suppuration, *Am. J. Surg.* **19** 49, 1933.

safe degree of tension. Still, pneumothorax may change the lobe and its ectatic bronchi from a vertical to a horizontal position and thus promote better drainage. Artificial pneumothorax often finds its use as a preparatory procedure to radical thoracic operations.

Medical treatment is of no value in cases of marked suppurative bronchiectasis with complete destruction of the bronchial wall, the sooner surgical treatment is used in such cases, the better are the chances for clinical improvement.

SUMMARY

Recent studies of the respiratory dynamics of the bronchi and their defensive or expulsive mechanism are briefly reviewed, and the physiopathologic changes which may precede or accompany bronchial dilatation are discussed with especial reference to their diagnostic significance in early bronchiectasis.

Six distinct morphologic types of bronchial dilatation five of which are bronchiectatic and one of which is bronchiolectasis, are described as visualized roentgenologically after the intrabronchial injection of iodized oil. They are the tubular, cylindric, varicose and globular types, bronchiolectasis and bronchiectatic abscess.

The various theories concerning the mode of production of the polymorphic varieties of bronchiectasis are advanced, and the probable pathogenesis of each type is discussed. The tubular form may result from prolonged irritation of the bronchial mucosa, sclerotic and degenerative changes of the myo-elastic layers are considered to be the primary lesion in the cylindric form. The varicose type is, as a rule, brought about by massive pulmonary emphysema or atelectasis, whereas a diffuse bronchopulmonary distribution of fibrosis may entail bronchiolectasis, the globular type is only a segmental pouching occasioned by local weakening in the bronchial wall, and the primary bronchiectatic abscess is initiated by suppurative lesions in the bronchi.

Each of these morphologic types reveals itself clinically by a different mode of onset, a variable train of symptoms and certain physical signs. The clinical history is of greater diagnostic value than are the physical signs. Further studies and closer correlation between symptoms, signs and morphologic aspects as outlined by iodized oil in the living will no doubt enable us to draw a sharper line of clinical demarcation between the various forms.

No diagnosis of bronchiectasis is complete unless the location, the distribution and, above all, the type have been determined, for on this information often depends the therapeutic procedure to be followed. The indications for certain therapeutic measures in the various types are briefly discussed.

OSTEOMALACIA

NECROPSY OBSERVATIONS IN A MAN

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AND

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CHICAGO

Interest in the group of diseases characterized by diffuse demineralization of the bones has been stimulated within the last decade by the increase in knowledge of calcium metabolism brought about by the studies of Aub and his co-workers, by the demonstration of the rôle played by vitamin D and, notably, by the discovery of parathormone. The preparation by Collip¹ of a potent extract of the parathyroid glands made possible the establishment of clinical criteria for the diagnosis of hyperparathyroidism. That Recklinghausen's disease (osteitis fibrosa cystica) is due to parathyroid tumor and is relieved by parathyroidectomy was first demonstrated by Mandl,² subsequent investigations have established that the clinical symptoms of this disease are dependent on hyperparathyroidism.

Genuine osteomalacia is a rare disease, particularly in males. Recent studies indicate that deficiency in vitamin D is primarily responsible. The metabolic changes characteristic of hyperparathyroidism have not been demonstrated. Enlargement of the parathyroid glands may, however, be present. Hypertrophy and hyperplasia, first described in cases of osteomalacia by Erdheim³ in 1906 and interpreted as an effect of the disease, have been reported in many but not in all cases. The observations at necropsy in a severe case of long standing seem of interest.

From the Departments of Pathology and Medicine, Northwestern University Medical School

1 Collip, J B. The Extraction of a Parathyroid Hormone Which Will Prevent or Control Parathyroid Tetany and Which Regulates the Level of Blood Calcium, *J Biol Chem* **63** 395, 1925

2 Mandl, F. Therapeutischer Versuch bei einem Falle von Osteitis fibrosa generalisata mittels Extirpation eines Epithelkörperchentumors, *Zentralbl f Chir* **53** 260, 1926

3 Erdheim, J. Tetania parathyreopriva, *Mitt a Grenzgeb d Med u Chir* **16** 632, 1906

REPORT OF CASE⁴

The patient was a white man whose parents were Americans in average circumstances. The first sign of the disease, pain and deformity in the chest, appeared when he was about 19 years of age. Pains in the back, chest and hips became severe about three years later and led him to seek medical advice. At this time the deformity in the chest was marked. A history of a deficient diet could not be obtained. Treatment for a year produced no improvement. In 1911, when the patient was 23 years of age, castration was performed. The testes were normal. Prolonged treatment with phosphorus, trials of thyroid extract, extract of the posterior lobe of the pituitary gland and epinephrine and adherence to a general diet to which were added large amounts of milk and leafy vegetables, resulted in subjective improvement, which was maintained for the next ten years so that he was able to carry on his work of watch repairing. He was unable, however, to walk without crutches. The condition of the bones remained unchanged as determined by clinical and roentgen examinations. Repeated physical examinations during this period revealed only the characteristic softness of the bones and the resulting deformity. No palpable enlargement in the thyroid region was ever observed. The basal metabolic rate was normal, and symptoms of hyperthyroidism were lacking except for a brief period following the use of extract of thyroid gland. The patient was last examined in 1921. A severe infection of the upper respiratory tract in January, 1928, was followed by cardiac decompensation. After seven weeks in bed he died in March, 1928, at the age of 40. Roentgenograms of the chest, spine, pelvis and extremities made post mortem showed an extreme loss of calcium, much more marked than had previously been observed, and an absence of cysts or tumors in the bones (fig 1).

Necropsy—The body was that of a poorly nourished white man, appearing to be much younger than the actual age given (40 years). The length of the body when the knees were forcibly extended was about 59 inches (150 cm), the weight was about 90 pounds (40.9 Kg). The upper part of the thoracic spine showed a prominent kyphosis which extended backward and to the right, the lumbar vertebrae a compensatory lordosis and scoliosis. The anterior wall of the chest presented an exaggerated degree of pigeon breast deformity. The horizontal ram of the pubis were bent inward, producing a beaklike prominence of the symphysis and an extremely narrow pubic arch. There was a lateral angulation of the right humerus at the junction of the middle and lower thirds, and the left humerus showed a similar, but less prominent, deformity. The proximal phalanges of both hands were in the position of hyperextension. The metacarpophalangeal joints and the knees and ankles were greatly enlarged. The loose knee joints and enlarged external condyles of the tibiae and femurs produced an apparent angulation at the knees, which were held in a semiflexed position by the shortened hamstring muscles.

The calvarium was extremely light weight, with resistance to sawing like that of soft, dry wood. In its thickest part it measured 8 mm and in its thinnest, 4 mm. A groove-like depression involving only the outer table of the left side of the frontal bone was located just beneath a thin scar of the forehead. Transverse sections through the femur and tibia about 20 cm and 25 cm, respectively, from the knee joint showed a soft, friable shell of bone from 0.5 to 1 mm in thickness.

⁴ A clinical description of this case was reported in 1917 (Elliott, C. A., and Nadler, W. H. The Effect of Castration upon Osteomalacia in the Male, *Am J M Sc* **153** 722, 1917).

The marrow consisted of yellow fat. The cancellous part of the bones near the joint was so soft that it could be indented with the thumb-nail. The bone of the vertebral bodies was somewhat firmer. The ribs were extremely soft and brittle. They could be cut smoothly with a knife, and some portions seemed to be completely decalcified. Enlargements which represented the sites of old fractures were composed of fairly dense rubbery fibrous tissue, but they were elastic, could be

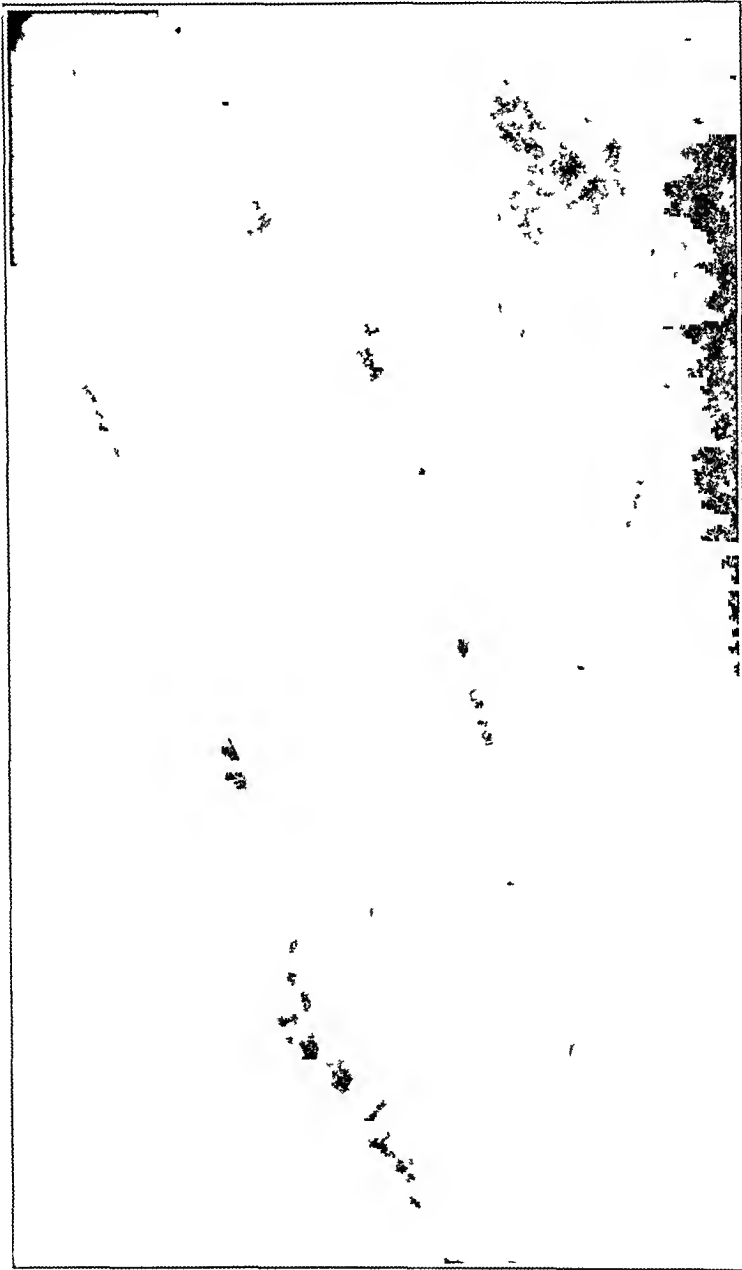


Fig 1—Roentgenogram of the right humerus showing the characteristic demineralization and a spontaneous fracture

compressed between the fingers and appeared to contain no calcium salts. Many of these were seen from the inside of the wall of the chest. Some were angulated, while others showed merely callus-like thickenings.

The endocrine glands revealed nothing of importance except slight hypertrophy of the hypophysis (0.95 Gm.) and hypertrophy of the two parathyroid glands. The thyroid gland weighed 28.5 Gm., was symmetrical and showed a homogeneous,

glistening, yellow-red parenchyma. On the posterior margin of each lobe, about 2 cm from the upper pole, was a yellow-gray parathyroid body outside the thyroid capsule. Their measurements were, respectively, 11 by 4 by 2 mm and 10 by 7 by 2 mm. The others were not visible on the surface, and serial free-hand sections made from 1 to 2 mm apart after hardening the gland in a solution of formaldehyde failed to reveal the other two parathyroid bodies. The suprarenal glands weighed 13 Gm together and on section showed a normal bright yellow and light brown cortex about 1 mm in thickness and a gray medulla in normal proportion. The pancreas was not remarkable. Both testes were missing and had been replaced by balls of paraffin.

The pathologic findings in the other organs and tissues are included in the following anatomic diagnosis: osteomalacia with extreme deformities of the spine, thoracic cage, pelvis and bones of the extremities, multiple old healed fractures of



Fig 2—A transverse section through the shaft of the tibia about 12 cm from the knee joint, to show the thin cortex and the reinforcing mass of cancellous bone in the anterior portion. The marrow is entirely fatty. The decalcified section was set in a concentrated form of pyroxylin. Hematoxylin-eosin stain, $\times 36$.

the ribs and humeri, hypertrophy of the two parathyroid glands, slight hypertrophy of the hypophysis, fatty degeneration of the myocardium, and hypertrophy and dilatation of the right ventricle of the heart, brown induration and compression atelectasis of the lungs, chronic passive hyperemia and moderate atrophy of the liver, bilateral hydrothorax, hydropericardium, chronic ulcer of the pyloric portion of the stomach, absent testes, and high grade general emaciation.

Histopathology.—Bones. Decalcified tissue was embedded in a concentrated preparation of pyroxylin and stained with hematoxylin and eosin and hematoxylin and carmine. Sections from the condyles of the femur through the articular cartilage showed a smooth, regular layer of eosinophilic hyaline cartilage on the outside which measured 1.5 mm in thickness. Near its inner margin was an interrupted

narrow band containing apparently normal cartilage cells with a purple matrix (calcified cartilage), a similar band of irregular patches of purple (calcified) cartilage formed a transitional zone between the hyaline cartilage and the bone. There was no regular bony cortex in this location, but merely the edges of irregular thick trabeculae of cancellous bone. The central part of the bone was formed of these irregular thick trabeculae and a fatty, fibrous marrow. Cellular marrow was found only in small islands in the zone of ossification, and the nucleated elements in these foci were chiefly nucleated red blood cells. The edges of the bony trabeculae were smooth in most places, and the borders were formed by wide zones

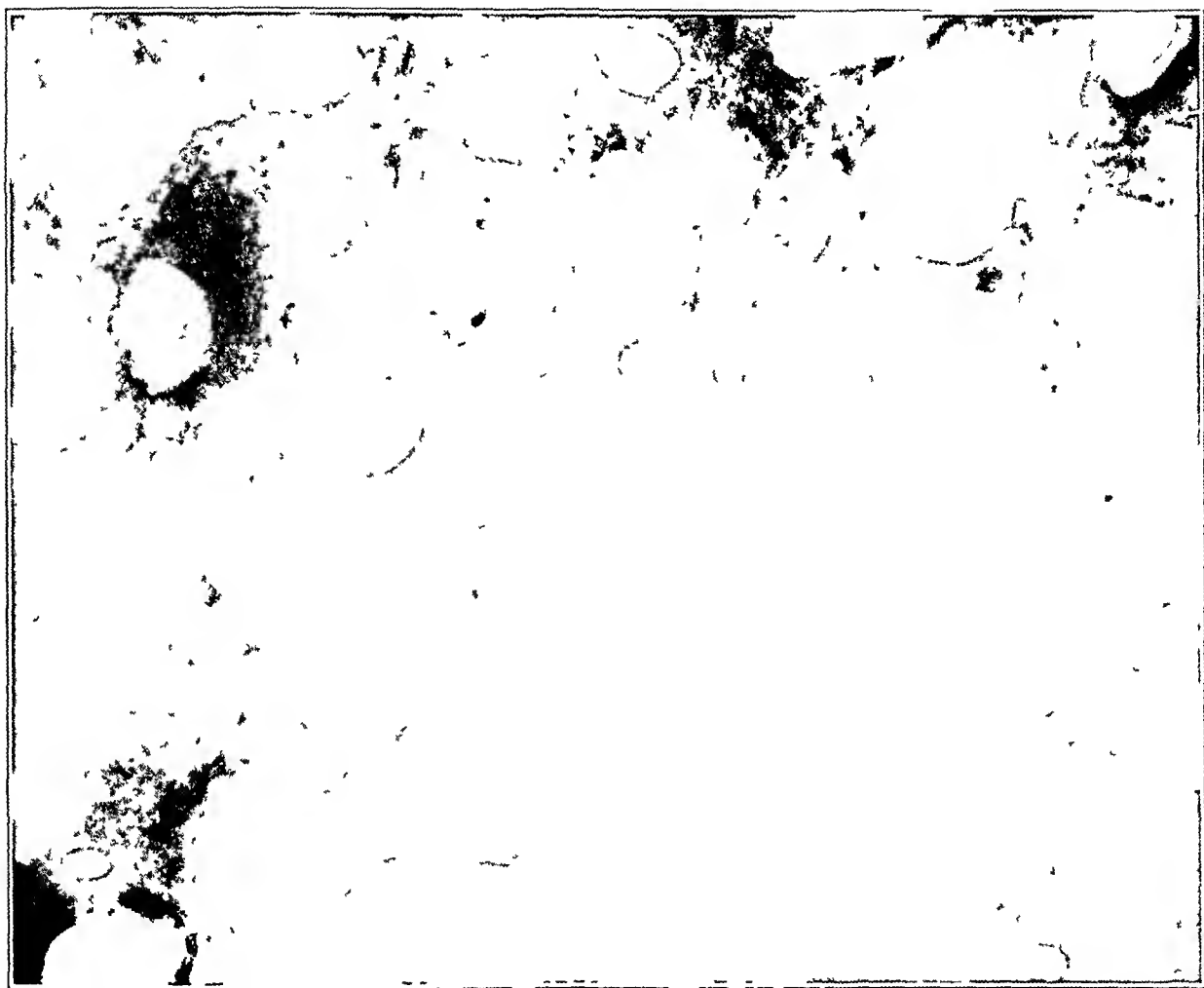


Fig 3—A low power ($\times 40$) photomicrograph of a cancellous portion of the tibia shown in figure 2. The light borders lining the trabeculae and surrounding the haversian canals are the calcium-free "osteoid seams."

of strongly eosinophilic bone laid down in regular lamellae. The middle zones of the trabeculae contained variously shaped, poorly defined areas that stained more or less strongly with hematoxylin (calcified areas). These calcified areas lay in regions that contained few Volkmann's canals, and in only a few places did they border on the medullary spaces. In general there was little evidence of active formation or destruction of bone. A few exceptions were found, however, in the form of large and small lacunae surrounded by bone with jagged edges, partly lined by regular rows of osteoblasts and showing nearby a few multinucleated giant cells (osteoblasts). The marrow in the lacunae was in some instances, fibrous and in others fatty with small hemorrhages.

Transverse sections of the tibia and femur showed a fairly dense cortex of varying thickness (from 0.5 to 1.5 mm). The periosteum was essentially normal and the periosteal surface of the cortex was smooth, while the endosteal line was wavy. In the thicker segments large medullary spaces were enclosed between the endosteal and periosteal lamellae. There was a greater proportion of calcified bone in these sections than in those previously described. The calcium-poor (eosinophilic) portions formed narrow zones along the endosteal surfaces and broader zones around the haversian canals and around most of the medullary spaces. Anteriorly the thin cortex of the femur was reinforced by cancellous bone of a

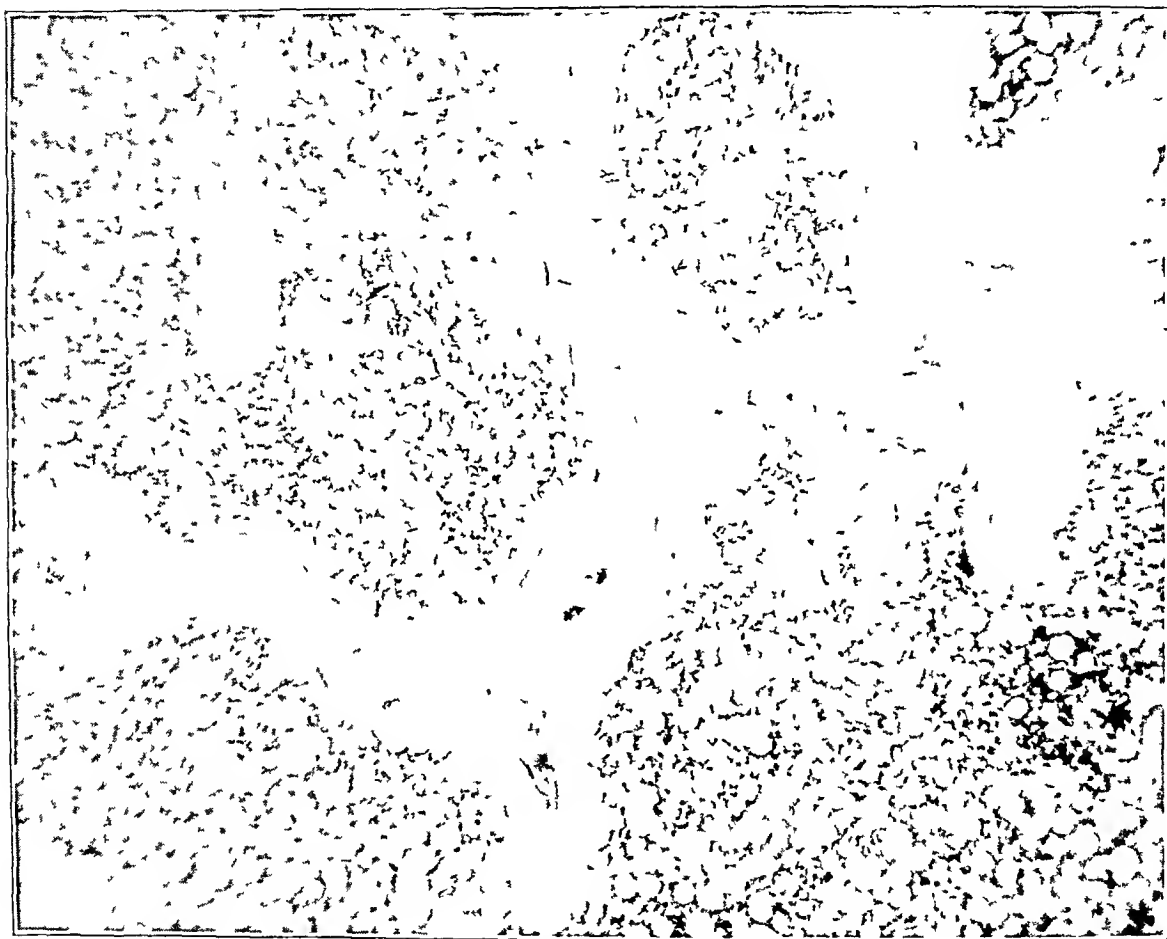


Fig 4—Photomicrograph ($\times 40$) of cancellous bone from a vertebral body. The "osteoid seams" are extremely wide. Only the dark patches along the middle portions of the trabeculae are calcified.

finer texture than that of the region of the condyles. The marrow consisted entirely of fat (figs 2 and 3).

The vertebral bodies (fig 4) were composed of very coarse anastomosing trabeculae which showed in their central portions narrow streaks and irregular patches of purple (areas of calcification) and broad zones of eosinophilic (calcium-free or calcium-poor) bone bordering the medullary spaces. The spaces contained a normal proportion of cellular marrow. Scattered through the marrow were poorly outlined masses of homogeneous purplish-gray acellular tissue resembling degenerated osteoid tissue. The zone of ossification between the cartilaginous plate

and cancellous bone was irregular, and in some places the intervertebral disk contained islands of poorly formed cancellous bone

Sections of the ribs made longitudinally through sites of old fractures showed dense callus consisting of broad, slightly calcified bony trabeculae, small islands of cartilage and poorly cellular fibrous tissue. On each side of the callus the marrow was unusually rich in hematopoietic tissue, within the callus it was largely fatty and fibrous

Heart Sections from the wall of the left ventricle and muscular septum showed swollen, granular muscle fibers with shrunken, irregular, hyperchromatic nuclei in many areas. In the right ventricle the degenerative changes were much more advanced. Between the pectinate muscles of the right auricle small thrombi were insinuated, in several places they were intimately attached to the endocardial surface. Frozen sections stained with sudan III and hematoxylin showed small irregular patches and stripes of yellow lipid substance intermingled with fewer coarse red granules of fat within the degenerated segments of muscle fibers. These areas of fatty degeneration were extremely numerous in the wall of the right ventricle and constituted as much as 50 per cent of the area represented

Lungs The parenchyma showed the effects of compression and stasis in the form of flattening of the alveoli, thickening of their walls and large numbers of macrophages and erythrocytes within the narrow alveolar spaces. Several foci of lymphocytic infiltration were found near the small bronchi

Liver The most prominent histologic changes appeared in the parenchyma around the dilated central veins. The hepatic cords around them were extremely slender and in many instances had disappeared, leaving only the radially arranged sinusoidal endothelium and granular cellular debris. The remaining cells had pyknotic nuclei and scanty cytoplasm filled with finely granular brown pigment. A large number of the hepatic cells in the intermediate zone contained small vacuoles, but at the peripheries of the lobules they were essentially normal

Spleen and Kidneys There was a slightly increased density of the fibrous reticulum in the spleen. The sinusoids were moderately distended with blood. The glomeruli of the kidneys were uniformly large. The convoluted tubules showed a moderate to high grade granular degeneration, with thinning of the epithelium, pyknosis of many of the nuclei and much granular detritus in the lumens. The cortex contained numerous small calcareous deposits, most of which appeared to lie within lymph channels, sometimes near a glomerulus and occasionally at some distance from any glomerulus in the section. A few clumps were found between the collecting ducts in the papillae

Suprarenal Glands In routine sections stained with hematoxylin and eosin the cortex showed nothing abnormal. The chromaffin tissue of the medulla was unusually abundant. Frozen sections stained with hematoxylin and sudan III showed abundant stainable lipid substance throughout the cortex, many of the coarser droplets had the staining reaction of neutral fat

Hypophysis In the anterior lobe the sinus-like blood capillaries were widely dilated (postmortem settling?). In general the chief cells predominated. Near the center of the lobe eosinophilic and chief cells appeared to be in about equal numbers, while at the periphery the latter constituted by far the greater part of the parenchyma. The basophilic cells were concentrated in poorly outlined masses in the anterior and inferior part of the lobe near its apex, and their number was relatively very small. Tissue fixed in a solution of formaldehyde and stained with ethyl-violet-orange G after mordanting in potassium dichromate yielded essentially the same findings as tissue stained in hematoxylin and eosin after fixation in

Zenker's solution to which a solution of formaldehyde has been added. No differential counts were made of the specifically stained cells since careful comparisons with sections of normal hypophyses demonstrated to our satisfaction that this picture was well within the limits of normal variation. The pars intermedia was not well developed and was represented by only a few follicles containing colloid substance and was lined by a single layer of low cuboid epithelium. The pars nervosa showed no noteworthy changes.

Pineal Gland The structure was that of a normal adult gland, with masses of calcareous matter near the line of junction between the pedicle and the glandlike structures.

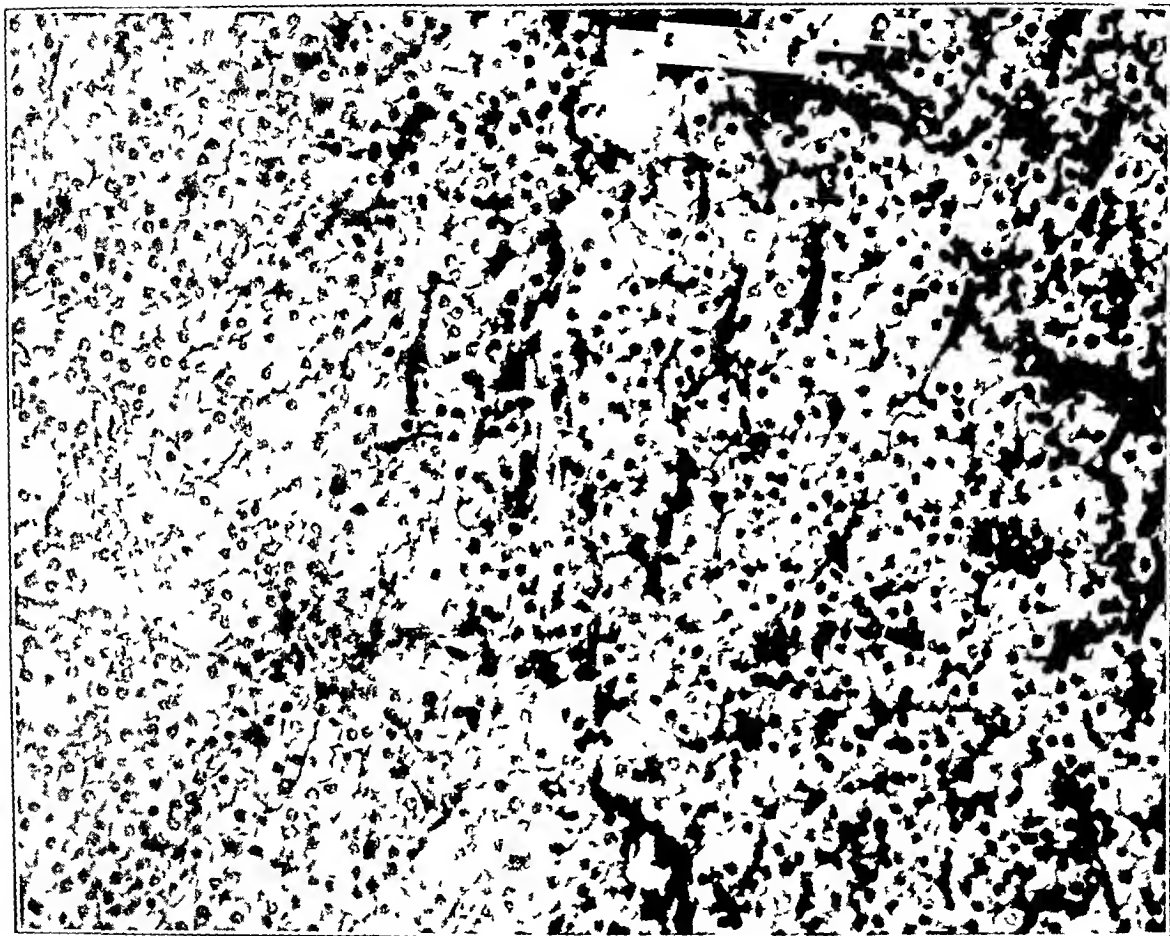


Fig 5—A high power ($\times 200$) photomicrograph of a section of one of the parathyroid glands. The chief cells predominate. A few scattered eosinophils are seen near the blood vessels as cells with dark gray cytoplasm.

Thyroid Gland This was essentially normal.

Parathyroid Glands Each of the two glands was completely surrounded by a delicate fibrous capsule, and the structure of the parenchyma did not differ appreciably from that of a normal parathyroid body. The polyhedral epithelial cells were packed together in solid lobules and cords, and in a few small areas alveolar structures were formed by columnar cells which differed only in shape from the polyhedral cells. The cytoplasm was clear or very finely granular. The nuclei were nearly round and dark and showed a sharp nuclear membrane and fine

chromatin granules. In a few small, poorly defined areas the cells were swollen and the cytoplasm was foamy or entirely clear. In other areas of similar extent but more sharply outlined the cytoplasm was strongly eosinophilic and finely granular. The eosinophilic cells were found also singly or in small groups scattered throughout the glands. Their nuclei were slightly smaller and darker than those of the predominant pale cells. Interstitial fat was very scanty as compared with the amount usually found in normal glands. Relatively large areas showed none. The usual close network of fine blood capillaries was found, the capillaries seemed neither more engorged nor less well filled than under normal conditions.

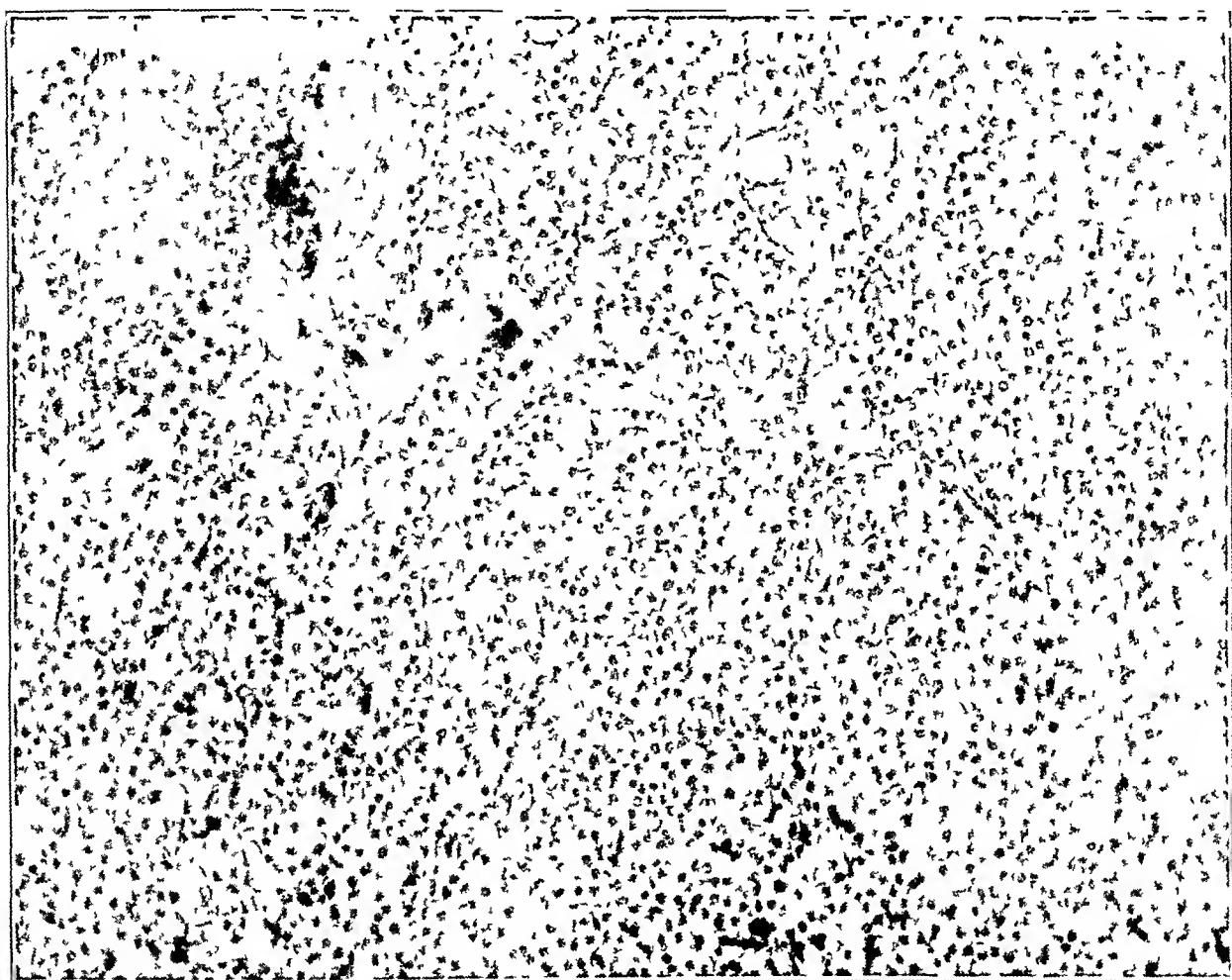


Fig 6—Another area from a section of the parathyroid gland, including a small mass of eosinophil cells in the upper right hand corner ($\times 150$)

COMMENT

This case of severe osteomalacia in a man apparently began at about the age of 19 and continued for twenty-one years. During eleven years of observation no significant findings other than the changes in the bones were observed. There was no palpable tumor in the region of the thyroid gland, evidence of hyperthyroidism was lacking. No history of dietary deficiency was obtained. Accurate clinical studies of the calcium metabolism were not possible prior to 1921 when the

patient was last examined. Castration in 1911 had no appreciable effect, in the week following the operation the excretion of calcium and phosphorus in the urine and feces was approximately the same as before the operation. The condition remained stationary for a number of years. Pathologic fractures occurred late in the disease. Death was due, probably, to heart failure. Necropsy showed fatty degeneration of the cardiac muscle, chronic passive congestion of the liver, parenchymatous degeneration of the kidneys, and generalized rarefaction and decalcification of the skeleton without formation of a cyst or tumor.

An unquestionable differentiation between osteomalacia and Recklinghausen's disease in certain cases does not appear to be possible on the basis of changes in bone alone. While in advanced cases of the latter disease cystic areas or brown tumors (hemorrhagic giant cell tumors) or both can usually be demonstrated, there are some cases in which these features are lacking.⁵ Histologically the wide osteoid seams of trabeculae, the absence of excessive fibrosis of the marrow and the relatively small number of osteoblasts in true osteomalacia tend to distinguish it from typical Recklinghausen's disease in which the osteoid seams are narrow, fibrosis of the marrow is a striking feature, and both osteoblasts and osteoclasts are numerous, frequently with the formation of giant cell tumors. However these differentiating features are only relative, and the degree of development of each depends on such factors as the intensity and duration of the disease, the diet of the patient and the therapeutic measures used. In a recent review of the subject of hyperparathyroidism Jaffe⁶ suggested that one of Erdheim's cases described in 1907,⁷ the first one of the series in which an enlarged parathyroid gland was shown, was not really one of osteomalacia but one of Recklinghausen's disease because of the narrow osteoid borders, fibrous marrow and numerous osteoblasts in the involved bones. In our case also some parts of the marrow were fibrous, and in a few areas both osteoblasts and osteoclasts were numerous, but the consistently wide osteoid borders would certainly furnish strong evidence that the case was one of osteomalacia and not of osteitis fibrosa.

In the case reported the glands of internal secretion were normal grossly and microscopically with the exception of the hypophysis and parathyroid glands. The hypophysis showed slight hypertrophy, but without selective hyperplasia of any one type of cell. The parathyroid glands were only two in number, each definitely enlarged, being 11 by

5 Bergstrand, H. *Acta med Scandnav* **54** 539, 1921.

6 Jaffe, Henry L. *Hyperparathyroidism (Recklinghausen's Disease of Bone)*, *Arch Path* **16** 63 (July) and 236 (Aug.) 1933.

7 Erdheim J. *Sitzungsber d k Akad d Wissensch Math naturw Kl Wien* **116** 311 1907.

4 by 2 and 10 by 7 by 2 mm as compared with an average normal size of 6 by 3 by 2 mm.⁸ Microscopically the only definite deviation from normal was the poverty of fat cells. Such a reduction of fat is generally considered evidence of hyperplasia of the parenchyma. The other measure of hyperplasia, originally used by Erdheim⁹ to demonstrate microscopic hyperplasia in glands of normal size or slight enlargement—i.e., the demonstration of lipid droplets in the parenchymal cells by treating the tissue with osmic acid after fixation in Altmann's fluid—was not utilized in this case as the two entire glands had been embedded in paraffin before it occurred to us that such treatment might be desirable. The foamy appearance of small clumps of cells in the paraffin sections suggested that a considerable amount of lipid had been present, and therefore it is unlikely that the degree of hyperplasia indicated by such a criterion is more than moderate. Furthermore, later work has cast doubt on the validity of such a criterion of hyperplasia, i.e., paucity of lipid in the presence of active hyperplasia.⁵

The presence in this case of slight calcareous deposits in the kidneys without associated necrosis of the cells is consistent with the findings reported in many other cases of osteomalacia. Frequently other tissues in which acid is excreted, such as the lungs and the stomach, have been similarly involved. The explanation is not clear. In *ostetis fibrosa* such precipitation of calcium is naturally considered to be related to hypercalcemia.¹⁰ In the cases of osteomalacia that have been studied, however, an elevated calcium level in the blood has not been observed at any stage. In cases in which no treatment has been given the negative calcium balance reported has been due chiefly to the increased elimination of calcium in the feces.¹¹ On a diet low in calcium, however, a urinary excretion of calcium greater than the intake has been observed.¹² It appears that in osteomalacia hyperplasia of the parathyroid glands represents a compensatory physiologic hyperactivity of these glands resulting in such gradual loss of bone calcium that hypercalcemia does not occur. The mechanism seems to be similar to that of experimental rickets in which deficiency of vitamin D causes hypertrophy and hyperplasia of the parathyroid glands. Prevention of hyper-

8 Cowdry, E. V., in Barker, L. F. *Endocrinology and Metabolism*, New York, D. Appleton & Company, 1922, vol. 1, p. 501.

9 Erdheim, J. *Beitr. z. path. Anat. u. z. allg. Path.* **33**: 158, 1903.

10 Bulger, H. A., Dixon, H. H., and Barr, D. P. *The Functional Pathology of Hyperparathyroidism*, *J. Clin. Investigation* **9**: 143, 1930.

11 Miles, L. M., and Feng, C. *Calcium and Phosphorus Metabolism in Osteomalacia*, *J. Exper. Med.* **41**: 137, 1925.

12 Gargill, S. L., Gilligan, D. R., and Blumgart, H. L. *Metabolism and Treatment of Osteomalacia*, *Arch. Int. Med.* **45**: 879 (June) 1930.

trophy of the parathyroid glands by the administration of parathormone in minor deficiency of vitamin D produced experimentally has been reported

The symmetrical enlargement and normal histologic appearance of the parathyroid glands in this case are convincing evidence that the condition was simple hyperplasia rather than neoplasia (adenoma). We are inclined to consider the hyperplasia compensatory in the sense of Erdheim and the majority of later authors. This is consistent with the findings in a number of cases of true osteomalacia reported in the literature since Erdheim's publications of 1906 and 1907. Such an opinion is supported by the fact that compensatory enlargement of the parathyroid bodies occurs frequently in other diseases associated with rarefaction of bone, such as rickets, senile osteoporosis, so-called hunger osteomalacia, chronic nephritis and both primary and secondary tumors of bone.

Clinically, hyperparathyroidism associated with parathyroid tumor has been proved to be an entity embracing Recklinghausen's disease. Conservative application of present knowledge limits the indication for parathyroidectomy to primary hyperparathyroidism. The persistence after operation of definite signs of the disease points to the presence of an undiscovered hyperfunctioning tumor. The tentative classification of other conditions of varied etiology, such as rickets, osteomalacia and loss of calcium from the bones in cases of hyperthyroidism and pregnancy, as secondary hyperparathyroidism has been confusing. It has been suggested that the parathyroid glands which progressively remove calcium from the bones in order to maintain a normal level of calcium in the blood may continue to remove excessive amounts long after the need has passed, and that excision of glands which prove to be normal on gross and microscopic examination is justifiable when clinical findings signify overactivity.¹³ From the information available, however, it appears unlikely that the removal of glands found to be normal will, *per se*, have a beneficial effect. The problem is one of accurate diagnosis and location of the tumor.

The diagnosis of osteomalacia depends (1) on the differentiation of primary hyperparathyroidism and (2) on the exclusion, in adults, of osteoporosis occurring in hyperthyroidism, senility, neoplasms involving bones, etc. In typical advanced cases of Recklinghausen's disease the following observations are diagnostic: a high level of serum calcium and an excessive excretion of calcium in the urine, a low concentration of serum phosphorus and an increased elimination in the urine, roentgenographic evidence of a diffuse loss of calcium

13 Hitzrot, L. H., and Comroe, B. I. Hyperparathyroidism Without Parathyroid Tumor. *Arch. Int. Med.* 50: 317 (Aug.) 1932.

from the bones, usually with formation of cysts or tumors, hypotonia and muscular weakness. Difficulty is encountered in early cases in which cysts or tumors of bone are absent. The parathyroid tumor involving one or more glands, is frequently not palpable, detection may require exposure of each of the glands. Persistent hypercalcemia associated with a lowered level of phosphorus is decisive. Hypercalcemia was consistently present in the seven cases of osteitis fibrosa observed by Bauer¹⁴. Under certain conditions of diet and therapy, however, the level of the blood calcium may not be elevated.⁶ Such cases require prolonged and carefully controlled metabolic studies.

That deficiency of vitamin D is the essential cause of osteomalacia is indicated by various studies. Miles and Feng,¹¹ in 1925, reported a marked seasonal variation in the severity of the condition in cases observed in China. They found a negative calcium balance in three of four cases, obtained good results with the administration of cod liver oil and calcium, and concluded that the disease was one of dietary deficiency in the same category as rickets. The case of Gaigill, Gilligan and Blumgart,¹² carefully studied for more than a year, showed a persistently normal level of blood calcium and a lowered level of blood phosphorus, a finding which is present also in rickets. A negative calcium balance persisted, even though the intake of calcium greatly exceeded normal requirements, until the patient was fed very large amounts of cod liver oil concentrate. The addition of irradiation with ultraviolet rays hastened the improvement. These results suggested that the condition was a form of adult rickets. Viosterol and calcium therapy have also been used with benefit.¹⁵

SUMMARY

The observations of necropsy in a typical case of osteomalacia in a man are presented and discussed. Besides the typical skeletal deformities, the pathologic changes of special interest were hypertrophy and hyperplasia of the parathyroid glands, slight hypertrophy of the anterior lobe of the hypophysis and numerous small calcareous deposits in the kidneys. Only two parathyroid glands could be found. These were equally enlarged and presented microscopic evidence of mild hyperplasia interpreted as a compensatory condition caused by increased physiologic activity.

14 Bauer, W. Hyperparathyroidism—A Distinct Disease Entity, *J. Bone & Joint Surg.* **15** 135, 1933.

15 Decourt, J., and Kaplan, S. Le traitement de l'osteomalacie par l'ergostérol irradié, *Paris méd.* **2** 485 (Dec. 3) 1932.

News and Comment

AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians will hold its nineteenth annual clinical session in Philadelphia from April 29 to May 3 1935. Announcement of these dates is made not only to apprise physicians generally of the meeting, but also to prevent conflicting dates for the 1935 meetings of other societies.

Dr Jonathan C Meakins, of Montreal, Canada, is president of the American College of Physicians, and will arrange the program of general sessions. Dr Alfred Stengel, vice president in charge of medical affairs of the University of Pennsylvania, has been appointed general chairman of local arrangements, and will be in charge of the program of clinics. Mr E R Loveland, executive secretary, 133-135 South Thirty-Sixth Street, Philadelphia, is in charge of general and business arrangements, and may be addressed concerning any feature of the forthcoming session.

Book Reviews

A System of Clinical Medicine Dealing with the Diagnosis, Prognosis, and Treatment of Disease, for Students and Practitioners By Thomas Dixon Savill, M D Edited by Agnes Savill, M D, assisted by E C Warner, M D Ninth edition Price, \$9 Pp 1,063, with 163 illustrations Baltimore William Wood & Company, 1933

The ninth edition of this system of clinical medicine makes its appearance twenty-eight years after the first edition was brought out. The work has evidently been well received and must have a certain amount of inherent merit to have survived so many editions over such a period of time and with the original editor supplanted by another. The book represents the work not of one man but rather of some seventeen contributors, who have prepared certain sections or revised certain portions. The list of contributors includes the names of some well known English physicians, names which are a guarantee of the reliability of the work.

The material is presented in rather an unusual way. The editor wanted to stress clinical medicine, therefore the classification of diseases is based largely on their clinical expressions. An excellent example is found in the classification of diseases of the lungs and pleurae. Roughly, these are divided into acute and chronic conditions and further subdivided into those that occur (1) without dulness on percussion, (2) with dulness on percussion and (3) with hyperresonance. Such a classification may call attention to, and accentuate, the most outstanding physical sign or symptom, but it makes for a jumbled hotchpotch which is unwieldy and which is dogmatic. Dogmatism is rife throughout the book, for example "A patient complains of pain in the gall-bladder region, pain is paroxysmal or dull and continuous, and radiates to the right shoulder. There is tenderness over the gall-bladder, vomiting and some fever. The disease is acute cholecystitis." Such dynamic diagnoses may make medicine simple to the student, but, unfortunately, in practice the diagnosis of pathologic conditions is not made with the ease implied in this statement and similar statements.

The book deals with many phases of internal medicine other than disease entities. It starts with a brief discussion of case taking and methods, a section on physical diagnosis follows. The discussion of each anatomic system is preceded by a brief account of the symptoms that arise as a result of disease of this particular system. Here and there some effort is made to explain the pathologic physiology of the underlying disorder. Elsewhere will be found a number of pages devoted to diets. Then comes a section giving general information concerning laboratory examinations, this is too brief to be of practical use, but it will give the reader who is unfamiliar with these examinations some understanding of their purpose and value. The concluding section deals with a list of about eighty-one prescriptions for all kinds of conditions, varying from a solution of lead with zinc to a tannic acid gargle and to an expectorant cough mixture for children.

The book decidedly gives one the impression of being old-fashioned, it is entirely too dogmatic to appeal to any one except the most inexperienced tyro in the study of medicine, on whose mental processes it might produce grave injury, it attempts to cover too much ground in too few pages.

Nature, M D By Richard Kovacs, M D, Clinical Professor of Physical Therapy, New York Polyclinic Medical School and Hospital Price, \$2 Pp 181, with 10 illustrations New York D Appleton-Century Company, 1934

This volume is one of the so-called Popular Health Series, volumes of which are being published from time to time by the Appleton-Century Company. It is an unassuming book, not too long, well printed and written, as the author states,

in the hope that laymen, as well as professional persons who are interested in the remedial uses of heat, water, sunlight, electricity, massage and exercise, will find the information offered helpful

It must be difficult to assemble a book dealing with medical matters which will interest the casually reading public and yet be of some use to physicians. This book has accomplished this task with a surprising degree of success. The ordinary physician in general, knows little about the details of physical therapy. Here he has a chance to learn something of the theory and practice behind the popular forms of treatment which nowadays he often prescribes for his patients. On the other hand, the layman will find nothing to pander to morbid curiosity. He is given straightforward and honest information in regard to matters now familiar to him from well planned advertising, such as electric baths, bottled sunshine and colonic irrigations. On the whole, the book is worth owning.

Alcohol Its Effects on Man By Haven Emerson M.D., Professor of Public Health Practice, Columbia University Price, \$1 Pp 114 New York D Appleton-Century Company, 1934

This manual has been written to provide school teachers and high-school and college students with authoritative information regarding the effects of alcohol on man, as these are now known to medical science. It is written with particular simplicity from a nonpartisan point of view, and the essential facts of the present knowledge regarding this subject are summarized.

The underlying purpose in preparing a book of this character is summed up in the concluding sentence. "If the school children of the next few decades are taught the facts about alcohol as these are known, through the use of the scientific and experimental methods of the medical and social sciences, they and their children will be in a position to determine a rational personal and governmental attitude towards commerce in, and beverage use of, alcohol, and they may then avoid the extremes of partisanship in argument the pitfalls of political exploitation of voters, and the misinterpretation of knowledge by commercial interest and the press which together have made so pitiful an exhibition of our people during the past twenty years. The book can be highly recommended and will be helpful to the readers for whom it is intended.

CHRONIC RHEUMATIC DISEASES OF THE SPINE

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The knowledge of chronic rheumatism has reached a stage in which a satisfactory classification based on pathologic changes, etiology and clinical manifestations can be made. Two types, distinguishable clinically, have been accepted: (1) rheumatoid arthritis, infective in origin, and (2) osteo-arthritis, a degenerative disease. Osteo-arthritis of the spine is exceedingly common; in fact, no other articulations are so frequently involved. The reason for this will be considered later.

A much discussed question is: Does rheumatoid arthritis attack the spine? As this disease begins in the synovial membrane and later destroys the underlying cartilage, it is not probable that it would attack the intervertebral disks which do not have a synovial membrane. However, the vertebrae have articulations anatomically identical with those of the extremities, namely, the articulations of the ribs and transverse processes, commonly referred to as the small articulations of the spine.

Investigation of rheumatic diseases of the spine is confined largely to the German literature and especially to the studies of the late Professor Schmorl of Dresden. In his pathologic institute he was given permission to remove the dorsal and lumbar spine at autopsy. He removed approximately 10,000 spines. Of these, 4,253 were macerated and studied carefully, Schmorl's work being carried on in conjunction with that of the roentgenologist Junghanns. Their observations have been reported in a recent monograph.¹ At the time the spine was removed it was carefully palpated for the presence of osteophytes, and if any were present their extent, location and size were recorded. This report covers only the observations on the 4,253 macerated specimens, 2,115 of which were from males and 2,138 from females. Schmorl found the age incidence to be the same in both sexes. This observation is at variance with that of others who have reported that the incidence is greater in males. Schmorl accounts for this variance on the basis that by palpation he was able to detect along the vertebral rim slight ridges or irregularities which might not show up in a roentgenogram. One may infer from Schmorl's observations that the incidence is the same in the two sexes, but that the condition occurs in a more advanced stage in the male.

1 Schmorl, G., and Junghanns, H. *Die gesunde und kranke Wirbelsäule im Roentgenbild*, Leipzig, Georg Thieme, 1932.

Osteophytes were not found on the spines of patients in the first two decades of life, they were present in 10.7 per cent of those in the third, in 36 per cent of those in the fourth, in 78 per cent of those in the fifth and in 93 per cent of those in the sixth decade. All writers have recognized the age incidence of osteoarthrosis of the spine. Schmorl claimed that the disease is degenerative in character and that it is the result of overuse.

The greater incidence of this disease in the spine indicates that the spine is subject to unusual strain. Apparently the spine of man has not adjusted itself to the upright posture. Schmorl believes that the cause of these early changes is due to a loss of resiliency in the disk. He referred to the observation made by Rokitsansky seventy-five years ago that the intervertebral disk loses its resiliency with advancing years.

Beneke² was one of the first observers to arrive definitely at the conclusion that the exciting cause of osteoarthrosis of the spine is degeneration of the disk. He was the first to observe that right-handed persons show more marked lipping on the right side of the lower dorsal and on the left side of the lumbar spine. The reverse is observed in left-handed subjects. The strain of lifting produces tension on the ligaments of the right side of the lower dorsal spine with a consequent development of osteophytes at the points of attachment of these ligaments.

Schmorl has studied the formation of the disk from embryonic life up through the advancing years. After he removed a spine it was his practice to sever the intervertebral ligaments and to observe the rebound of the disk when freed from the pressure of the vertebrae. He observed that in not all instances of loss of resiliency is there evidence of lipping.

Schmorl then made a careful study of the structures in the disk. The substantia spongiosa of the articulating surface of the vertebra is covered by a hyaline cartilaginous plate. The disk proper consists of two distinct structures with a marked anatomic similarity: the annulus fibrosus fibrocartilagineus intervertebralis and the nucleus pulposus. The annulus fibrosus is made up of concentric lamellae of fibrous tissue with fluid in the interstices. These fibers run obliquely in a curved line from one vertebral rim to the rim of the adjacent vertebra where they fuse with the anterior and posterior longitudinal ligaments. The fibers of these ligaments are attached to the vertebra. This attachment begins at the rim. As the anterior ligament is the larger, the attachment to the vertebra is more extensive. The arrangement of the fibers of the annulus varies at different levels of the spine to meet the needs for tension and extension at the various levels.

² Beneke, Rudolph. *Beitr. z. wissensch. Med.* 1: 109, 1897.

Beadle³ said, "The course and attachment of the fibers of the annulus suggests a guy rope whose function is to maintain the proper relationship of the vertebrae to each other." The strain of torsion and extension is borne largely by these fibers. Vertical shock is borne by the nucleus pulposus. The inability of the disk to adjust itself to this strain, in conjunction with its poor nutrition, probably accounts for the early appearance of degenerative changes. The disk is not vascularized but receives its nourishment by a process of diffusion from the substantia spongiosa of the vertebra.

The nucleus pulposus is embedded in the annulus and, except early in life, is not easily differentiated from it. It is spherical, located slightly posteriorly to the center of the disk. When normal it is slightly thicker than the disk, and in some instances causes a slight local bulging when the ligaments between the vertebrae are severed. It blends into the surrounding annulus. Structurally it differs only slightly from the annulus—the fibers are finer and more meshlike in their arrangement, and the matrix contains more mucoid material. It is more resilient than the annulus, it functions with the annulus as a cushion or shock absorber, it also increases the ease of rotation.

The earliest degenerative changes in the disk appear in the nucleus pulposus. It loses its fluidity, the fibers become desiccated and finally disintegrate. The elastic ball is replaced by a solid mass which at times shows evidence of calcification.

Somewhat later the annulus undergoes similar degenerative changes. As a result of this degeneration the disk is thinned and loses its resiliency. Furthermore, the fibers of the annulus play an important rôle in the fixation of the vertebra. As a result of these changes there is increased mobility of the involved vertebrae. Schmorl said that he had never seen osteophytes or lipping adjacent to a normal disk, although there may not be a close correlation between the degree of lipping and the degree of degeneration of the disk. The increased mobility of the spine is the most important factor in the formation of osteophytes. This increased movement, plus a thinning of the disks, may result in impingement of the vertebral rims—a form of trauma that would readily lead to the formation of osteophytes. A second factor, which Schmorl believes to be the more important, is the increased strain on the vertebral ligaments as a result of increased mobility. This strain on the anterior longitudinal ligament may give rise to irritation of the periosteum at the ligamentous attachment, with the formation of new bone. In some cases the outgrowth of bone is not confined to the vertebral rim but extends along the course of insertion.

3 Beadle, O. A. *The Intervertebral Discs. Observations on Their Normal and Morbid Anatomy in Relation to Certain Spinal Deformities*, Medical Research Council, Spec. Rep. Ser. no. 161. London, His Majesty's Stationery Office, 1931.

or attachment of the ligament. This is additional evidence that traction plays a rôle in the development of osteophytes. Schmorl believes that this factor explains the absence of osteophytes on the posterior surface of the vertebrae as the posterior longitudinal ligament is only slightly attached to the bone, its main attachments being to the posterior edge of the intervertebral disk.

Anton Fischer stated that the formation of osteophytes is an effort to reconstruct a spine which has become functionally inefficient. The primary objective of the formation of osteophytes is to effect a bridging. In addition to the osteo-arthritis—the result of long continued mild trauma—an acute trauma may produce similar changes. This acute trauma is not necessarily a blow, the same changes may follow a localized infection of a vertebra. Following an acute injury, when there is no evidence of fracture which might be responsible for traction or strain, osteophytes may develop on the injured and adjacent vertebrae, and complete bridging may follow. Perhaps this is a purposeful physiologic reaction to repair injury.

Following typhoid fever a sharply localized osteomyelitis demonstrable in the roentgenogram may develop in a vertebra. A later examination may show complete bridging in the involved area. In the few cases of this character that I have seen there was evidence of severe damage to the disks. In one case, with localized staphylococcic osteomyelitis involving a lumbar vertebra, a roentgenogram taken after the lesion had healed revealed bridging of the involved and adjacent vertebrae, but with an apparently normal disk. Changes of this character have been used as an argument that osteo-arthritis may be due to an infection. The infection, however, merely damages the vertebra and is only indirectly the etiologic factor in the osteo-arthritis.

The large majority of people with osteo-arthritis of the spine are free from discomfort. A few suffer from root pains. No satisfactory explanation for these pains has been presented except pressure of the osteophytes on the nerve. Anton Fischer said emphatically that pressure is not a factor, but he did not state the grounds for this conclusion and did not offer any acceptable explanation. He suggested that myalgia, due to an effort of the spinal muscles to immobilize the spine, may be responsible for some of the discomfort.

Spondylitis ankylopoietica or, as it is frequently called, spondylarthritis ankylopoietica is the second form of chronic rheumatism of the spine. It may produce the following pathologic changes: bony ankylosis of the small articulations of the spine, osteoporosis of the immobilized vertebrae, ossification of the spinal ligaments, especially of the anterior longitudinal ligament, development of spongy bone in the portion of the disk adjacent to the spongiosa of the vertebra and occasionally ossification of the periphery of the disk. Apparently not in all cases

does the disease advance to the point at which all these pathologic changes are present

All the writers whom I have consulted, with the single exception of Krebs, have claimed that the disease begins in the small articulations. Krebs⁴ stated that he has seen cases in which the roentgenograms show normal interarticular spacing of the small articulations. Furthermore, he stated that in a few cases he has made an incision down to these articulations and found them normal. Credit is usually given to Bechterew for the first clinical description of this disease. The case he described, however, was certainly not typical, as one of the symptoms was paralysis of the extremities with atrophy. Strumpell, and at about the same time Pierre Marie, described typical cases, but they believed that the disease always began in the lower part of the spine and extended upward. They both mentioned an associated ankylosing arthritis of the extremities. Frankel⁵ gave the best early account of this disease and showed that it may involve any portion of the spine and that it may be either localized or extensive. He observed that the small articulations may show bony ankylosis without ligamentous ossification. He expressed the opinion that the disease begins in the small articulations. In 2 of his 4 cases there was an ankylosing arthritis of the extremities and in 1 case, ankylosis of the temporomaxillary articulation.

There is a dearth of American literature on this subject. The early contribution by Elliott⁶ is an exception. He stated that Virchow was the first to describe two different diseases responsible for ankylosis of the spine—one due to exostoses with bridging, the other, to ankylosis of the small articulations and ossification of the ligaments. Elliott referred to the frequency of ankylosing arthritis of the extremities in this disease. In 1 of his 5 cases the disease in the spine followed an ankylosing arthritis of the extremities. The other 4 cases followed gonorrhea and showed no involvement of the joints of the extremities.

The development of typical rheumatoid arthritis of the extremities, in conjunction with these spinal changes, is good evidence that rheumatoid arthritis may involve the spine, and the pathologic change that follows is spondylitis ankylopoietica. The various pathologic changes appear to be directed toward immobilizing the spine. The disease is most prevalent during the third and fourth decade, resembling, in this respect, rheumatoid arthritis.

The incidence of this disease outside of special clinics for patients with rheumatic conditions is not very great. From among 10,000

4 Krebs, Walter. *Rheumaproblem* 2:163, 1931.

5 Frankel, E. *Fortschr a d Geb d Rontgenstrahlen* 7:62, 1904.

6 Elliott, G. R. *Am J Orthop Surg* 3:305, 1905.

autopsies Schmorl reported only 8 cases. On the other hand, Anton Fischer in his special clinic found 98 cases during a period of five years. Buckley⁷ reported 60 cases. It is a disease chiefly confined to the male sex, only 6 patients in Buckley's series were women. Freund⁸ stated that in the review of the literature he found only 1 case reported in the female sex. In this respect the disease differs from rheumatoid arthritis. Buckley made a sedimentation test on 23 patients, in all the rate was definitely increased.

Bachman⁹ reported 60 cases in the course of sixteen years, during that time he examined 2,561 spines. He emphasized the frequency with which the sacro-iliac ligaments are involved when the disease attacks the lumbar spine. He referred to a case in which the symphysis pubis was involved. All the recent German writers refer to the increased frequency of this condition in soldiers during the late war. This is probably accounted for by the prevalence of acute infections.

Rarely does the disease involve the entire spine. Involvement of the cervical spine is least frequent. In Fischer's series the lumbar spine was involved in 96, the dorsal spine in 89, the cervical spine in 54 and the sacro-iliac spine in 79 per cent of the cases. In practically all the cases which showed involvement of the hip joint there were associated sacro-iliac changes. Frequent reference is made in the literature to arthritis in the hip in cases in which the spondylitis occurs in the lower part of the lumbar spine. The rather infrequently reported incidence of this disease in America may possibly be explained by the fact that spondylitis ankylopoietica is mistaken for osteo-arthritis with bridging. Anton Fischer referred to reports in the literature in which it was stated that this disease developed in more than one member of a family. He observed an instance in which for two generations it appeared in two sisters.

ETIOLOGY

The disease is infective, but is not due to a specific micro-organism or to any special group of bacteria. Evidently a great variety of bacteria are capable of producing the characteristic changes. Twenty-nine per cent of Fischer's cases showed rheumatoid arthritis in the extremities. In this group the pathologic changes in the spine were probably due to streptococci. In 14 per cent of these cases there was a previous history of acute arthritis. Many cases have followed gonorrhea, and it is assumed that the gonococcus can produce the changes peculiar to the condition. The disease occasionally follows rheumatic fever, bacillary dysentery or typhoid fever. In some instances sepsis

7 Buckley, C. W. *Brit. M. J.* 1 1103, 1931.

8 Freund, Ernest. *Gelenkerkrankungen*, Berlin, Julius Springer, 1929.

9 Bachman, A. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 42 501, 1930.

is responsible for the condition. In 1 case the disease followed undulant fever.

It is perhaps unnecessary to state that a patient with spondylitis ankylopoietica does not necessarily have a rheumatoid arthritis of the spine. It may be said, however, that rheumatoid arthritis involving the spine leads to pathologic changes recognized as spondylitis ankylopoietica.

In 29 per cent of Anton Fischer's series of 98 cases, the trouble began with a gradual swelling of the joints of the extremities—a typical rheumatoid arthritis. (Whether rheumatoid arthritis is ever confined to the spine has not been proved and is very difficult of proof.)

SIGNS AND SYMPTOMS

Pain and stiffening of the spine are the earliest manifestations. The intensity of the symptoms depends on the acuteness of the onset. In some cases, stiffening of the spine, rather than pain, is the chief complaint. When the onset is acute (as in 2 cases recently seen by me) the pain along the spine may be excruciating, and the entire spine may be held rigid. Breathing is restricted and painful, and there is a girdle-like feeling about the chest. There may be severe pains in the extremities. On account of sciatic involvement there may be a positive Kernig sign. Pressure lateral to the spine or tapping of the spinous processes is painful. The tenderness may be more marked on one side of the spine. This pain is thought to be due to direct involvement of the nerve trunks in the inflammatory process. On awakening the patients may have a flaccid paralysis of an extremity which gradually subsides on change of posture. Areas of analgesia and hyperalgesia, corresponding to nerve distribution, can be demonstrated over the trunk and extremities.

These acute symptoms may persist for several weeks, with moderate fever and leukocytosis. The pain and tenderness, except along the spine, gradually subside. Still later, although the entire spine appeared involved, the tenderness and rigidity become distinctly localized. After ankylosis develops the chest becomes fixed, and respiration is entirely diaphragmatic. When the involvement is in the lower dorsal spine, the patient finds a kyphotic position most comfortable, and he gradually acquires a true kyphosis without lumbar lordosis. Bending, especially sideways, may be very painful. Marked rigidity of the spinal group of muscles is always present during the more acute stage of the disease. In active cases the sedimentation test is positive. Rarely is there any elevation of temperature, or at most it is very slight, and the same is true of leukocytosis.

The roentgen findings may not be apparent for many months or even for a year after the onset of symptoms. Krebs⁴ claimed that he had seen patients with stiff spines, in whom the stiffness had been present for several years, who had a positive sedimentation test, but a negative roentgenogram of the spine. Junghanns¹⁰ stated that if the interarticular space in the small articulations is visible the patient does not have spondylitis ankylopoietica. Fischer said that another early change is osteoporosis of the involved vertebrae. This change is more readily recognized than the bony ankylosis of the small articulations. I have recently seen a roentgenogram showing an advanced stage of the disease, in which the density of the involved vertebrae was increased. Another early finding appearing when the process is in the lower part of the lumbar spine is a shading in the sacro-iliac region due to ossification of the sacro-iliac ligaments. When the anterior longitudinal ligament is involved the spine has the characteristic bamboo-stick appearance. The disks may show an increased density owing to the presence of spongy bone. Osteophytes are not found. Schmorl has described a fibrosis stiffening of the spine in which, probably owing to injury, the cartilaginous plates became vascularized, and this was followed by invasion of the disk by a firm fibrous tissue causing ankylosis. There is no ankylosis of the small articulations or ossification of the ligaments in this disease.

Rarely does a patient with spondylitis ankylopoietica show the maximum degree of possible pathologic changes. Whether the incomplete picture may later become complete, or whether in some of these cases the disease has become quiescent, has not been determined.

PROGNOSIS AND TREATMENT

The prognosis depends on the extent of the involvement. When this is localized in the dorsal region, disability is not extreme. When the dorsal and lumbar regions are involved, the degree of disability is great. Involvement of the lumbar spine, which practically always leads to lumbosacral ankylosis, causes a considerable degree of disability. The disease does not, however, shorten life.

While all spondylitis ankylopoietica is not rheumatoid arthritis, the method of treatment may be that used in rheumatoid arthritis. As the results of treatment of rheumatoid arthritis show the treatment to be only moderately successful, the outlook for good therapeutic results in spinal arthritis is not great. As this disease is usually the result of some generalized infection, the question of removal of foci is not so important. The usually slow onset suggests a low grade infection in which treatment has proved to be of little avail. In occasional cases

¹⁰ Junghanns Arch f klin Chir 166 120, 1931

in which the onset is acute, I have found that rest in bed with analgesics, as codeine or acetylsalicylic acid, to make the patient more comfortable until the acute process subsides, proved to be the most satisfactory treatment

SUMMARY

The two types of chronic rheumatism seen in the extremities may affect the spine. Rheumatoid arthritis of the spine is usually followed by pathologic changes recognized as spondylitis ankylopoietica. Following the description given by Schmorl¹¹ the cause of the early and frequent incidence of osteo-arthritis of the spine is discussed.

¹¹ A complete bibliography of chronic rheumatism of the spine may be found in the monograph by Schmorl and Junghanns¹

PERIARTERITIS NODOSA (NECROTIZING ARTERITIS) ASSOCIATED WITH RHEUMATIC HEART DISEASE

WITH A NOTE ON ABDOMINAL RHEUMATISM

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The availability for study of an unusually large number of cases of periarteritis nodosa has revealed a significant association of this derangement with rheumatic heart disease. In the last two years, of eight cases of typical periarteritis nodosa verified at necropsy, four presented conclusive evidence of rheumatic heart disease. This evidence consisted in all four cases of a history of rheumatic fever (1 e, acute polyarthritis accompanied by fever) and clinical findings of rheumatic cardiovalvular disease. Postmortem examination revealed characteristic gross and histologic features of rheumatic fever including in every case the presence of Aschoff bodies.

In addition to the eight cases just mentioned the records of the department of pathology of the Mount Sinai Hospital show that the diagnosis of periarteritis nodosa was made in five other cases, in which the characteristic lesions were discovered at postmortem examination. Two of these five cases ran a febrile course with arthritis and presented clinical evidence of rheumatic valvular disease. Postmortem examination revealed, in addition to periarteritis nodosa, a verrucous endocarditis of the mitral valve in both cases and a large thrombotic mass involving an aortic commissure in one of them. No Aschoff bodies were found in the myocardium. Both cases ran the febrile course of a general infection accompanied by clinical evidences of glomerulonephritis. In neither case was a positive blood culture obtained. These cases will be reported subsequently.

A study of the literature reveals that because of certain superficial resemblances, to be discussed later, cursory analogies have been drawn between periarteritis nodosa and rheumatic fever. In attempting such comparisons, observers have generally worked under the disadvantage of having only one or two cases of periarteritis nodosa available for study. Those who have offered casuistic reviews of the literature have been

From the laboratories of the Mount Sinai Hospital

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handicapped by inadequate or unsatisfactory data in the reports of earlier writers. Recently, students of rheumatic fever have made careful descriptions of arterial lesions, which in a few cases they have compared to those in periarteritis nodosa. We shall show later why these findings have been inconclusive. A few cases of periarteritis nodosa reported in the literature revealed, in addition to a history of arthritis, valvular or endocardial abnormalities which may have been of rheumatic origin. One case,¹ interpreted by the authors as "sepsis with arterial lesions," was probably an example of periarteritis nodosa with rheumatic fever (Aschoff bodies in the myocardium). These reports will be considered in detail after the presentation of four cases in each of which we believe we can demonstrate for the first time a definite conformity to the clinical and pathologic features of rheumatic fever and to the generally accepted criteria for periarteritis nodosa, including the clinical features associated with such cases. Special points of interest and significance are the presence in one case of malignant sclerosis, and in two others, of an attack of scarlet fever within two months preceding the immediate illness for which the patient was admitted to the hospital.

REPORT OF CASES

CASE 1²—*History*—R. S., admitted on March 20, 1931, a boy, 7½ years old, complained of heart trouble. Eight weeks before, he had a mild attack of scarlet fever. Five weeks before admission his temperature rose to 101 F, then to 103 and 104 F. Simultaneously he complained of severe abdominal cramplike pains, which lasted five days. Following these, he had migratory pains in the joints, with some limitation of motion, lasting for a week. He also had scrotal pain. A physician diagnosed the condition as rheumatic heart disease. There were gradually mounting fever, striking pallor, a hacking cough on expiration and shortness of breath even at rest.

Examination—Examination revealed moderate dyspnea, a striking pallor and cyanosis of the lips. The pharynx was injected and the lungs showed dulness and râles at both bases. The heart tones were of poor muscular quality, and percussion revealed the left border at the midaxillary line. A loud sawlike systolic murmur was heard over the precordium, maximal in the fifth interspace beyond the mid-clavicular line, transmitted to the right and heard posteriorly over the right as well as over the left side of the chest. The liver was palpable two fingerbreadths below the costal margin.

Clinical Impression—The diagnosis was rheumatic carditis with mitral insufficiency and myocardial failure.

1 Strang and Semsroth. Streptococcic Septicemia with Vascular Lesions, Arch Int Med 47:583 (April) 1931.

2 In the first case only positive findings will be given. In the others details are omitted when they are identical with those in the first case. Case 1 was reported in a survey of periarteritis nodosa in children by Rothstein and Welt (Am J Dis Child 45:1277 [June] 1933).

Course—The temperature ranged between 100 and 104 F and the pulse rate between 120 and 140. A definite diastolic murmur developed and a pleuropericardial rub was heard. A roentgenogram of the chest showed enlargement of the heart, suggesting mitral disease, and congestion of the lungs. A blood culture was sterile, and the urine had a low specific gravity. The blood showed a hemoglobin content of 38 per cent, and 2,400,000 erythrocytes and 16,000 leukocytes per cubic millimeter, with 81 per cent polymorphonuclear cells, 17 per cent lymphocytes and 2 per cent monocytes. Increasing decompensation was followed by death in cardiac failure on April 9.



Fig 1 (case 1) —Arteritic lesions in the lung. Note the thickened vessels with gaping lumens and the vascular streaks with miliary nodules.

Autopsy—The diagnosis was periarteritis nodosa involving the lungs, kidneys, coronary arteries and external iliac artery, chronic cardiovalvular disease, mitral stenosis, and subacute rheumatic verrucous endocarditis.

Gross Examination—The right pleural cavity contained 500 cc of thin straw-colored fluid. The lungs revealed localized fibrinous pleuritis and moderate collapse of the lower lobes. A cut section showed numerous streaks spreading like cotton threads from the hilum of the lung (fig 1). Along these streaks were numerous tiny miliary nodules varying from the size of a pinpoint to less than that of a pinhead, shown on frozen section to be related to blood vessels. The streaks, on being cut across, appeared as thickened branches of the pulmonary vessels.

The heart revealed definite fibrinous pericarditis near the origin of the pulmonary artery and the aorta. The left auricle was somewhat dilated. There was an old healed lesion on the posterior auricular wall. There was a continuous verrucous endocarditis over the entire closure line of the mitral valve, forming an uneven shelf on the posterior cusp. A few pinhead-sized verrucae were present also on the aortic flap. The chordae tendineae were slightly thickened and in places showed slight fusion. The aortic cusps were rounded and showed discontinuous verrucae on the closure lines. The left ventricle showed tigering.

The liver showed an indistinct lobular structure with a cloudy appearance. The arteries were thicker than normal. Numerous reddish spots (blood vessels) on the surface of the kidneys corresponded to streaks in the cortex. Branches of the renal artery as they entered the medullary-pelvic junction were distinctly thicker and more rigid than normal. The mesenteric lymph nodes of the small intestine were enlarged. The aorta appeared to be normal, although a branch of the external iliac portion was difficult to probe.

Microscopic Examination ³ The left auricle of the heart showed a severe inflammatory lesion with swelling and necrosis of the collagen fibers. The endocardium showed an elastica-free reduplication of connective tissue with infiltration by histiocytes, lymphocytes and polymorphonuclear cells. The myocardium showed interstitial inflammation with polymorphonuclear cells. The mitral valve contained newly formed capillaries and was infiltrated by cells. The ring of the mitral valve also contained small vessels and inflammatory cells. There was a small amount of verrucous material in the pocket formed with the chorda tendinea. The endocardium of the valve showed thickening, with subendothelial elastica-free reduplication. There was a small hyaline verruca at the tip of the mitral valve. The myocardium contained numerous Aschoff bodies with swollen collagen and large basophilic cells with irregular margins and owl-eyed nuclei. There was an organized fibrous pericarditis contiguous with the ring of the mitral valve. A large branch of a coronary artery showed a periarteritic inflammatory lesion without much necrosis. The aortic valve showed early interstitial valvulitis. The right auricle showed an interstitial myocarditis with occasional Aschoff bodies. The tricuspid valve contained a typical rheumatic inflammatory lesion of the ring with inflammation of the vessels and infiltration by cells. The right ventricle contained foci of lymphocytes and numerous Aschoff bodies, mostly perivascular. The pericardium showed slight fibrinous pericarditis. There were large vessels in the pericardium showing proliferation and necrosis. The aorta disclosed a necrotizing periarteritis of the vasa vasorum in the adventitia.

The lungs showed marked atelectasis. The most striking changes, however, were in the vessels, which showed extensive involvement by a necrotizing and proliferative process, with recent and old lesions (fig 2). The recent lesions consisted of swelling of the media and adventitia, with necrosis of the former and replacement by a band staining deeply with eosin, sometimes completely circular, sometimes horn-shaped or semicircular. This band in some instances lay near or included smaller vessels and appeared to lie just beneath the endothelium. The distinction between intima and media was frequently lost. There was a marked cellular infiltration within the adventitia and periadventitia consisting of polymorphonuclear cells, lymphocytes and larger mononuclear cells, as well as a moderate number of eosinophils. Elastica stain showed an interruption, destruction and lamellation of

3 In the more recent cases standard sections of the heart were made according to the technic of Gross, Antopol and Sacks (A Standardized Procedure Suggested for Microscopic Studies on the Heart, Arch Path 10:840 [Dec] 1930)

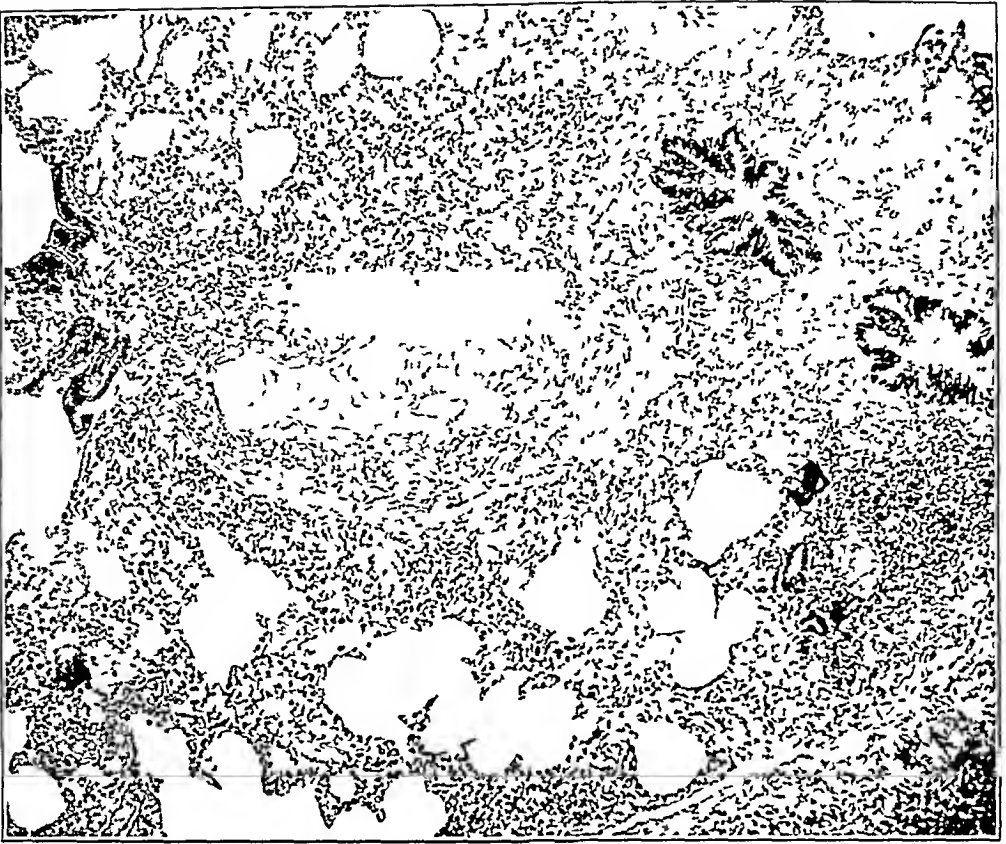


Fig 2 (case 1) —Necrotizing arteritis in the lung The large vessel in the center shows the characteristic band of necrosis involving the media and subintimal region A small artery at the right shows marked periarteritis



Fig 3 (case 1) —Fragmentation and interruption of elastica in a large artery of the lung, Weigert-van Gieson stain

the internal elastic membrane (fig 3) The endothelium showed proliferation and desquamation, often with encroachment on the lumen In the older lesions there was marked replacement by granulation tissue with newly formed capillaries in the periarterial and adventitial tissue often extending throughout all the layers In some vessels the intima was so thickened as to leave only a slit for a lumen, and in one artery of moderate size there was also thrombosis with recanalization

Hyaline and colloid degeneration of the tubular epithelium were evident in the kidneys The arteries showed both acute and healed necrotizing proliferative lesions similar to those in the lungs The characteristic homogeneous deeply pink bands were again visible as well as the periarterial and adventitial infiltrations



Fig 4 (case 1) —Necrotizing arteritis in the gallbladder Note the incomplete band of necrosis in the media, the periarterial infiltration, the intimal proliferation and the incomplete closure of the lumen

The healed lesions led to marked thickening of the walls of the vessels Some of the veins showed parietal thrombi, the wall of the vein adjacent to an affected artery having become inflamed by propagation

The liver showed central congestion, many arterial lesions, mostly old, resembling those in the kidneys, and a number of old organized vascular thrombi The vessels involved were generally not those in the portal spaces, but the larger branches in the broad septums

The stomach contained characteristic lesions of the large arteries with fibrinoid degeneration of the media or the subendothelium and marked periarterial infiltration and organization One or two of the arteries in the perijejunal tissues showed healed lesions and one showed a characteristic necrotic lesion Occasional vessels in the mesenteric lymph nodes showed healed lesions with organized thrombi

One of many sections of the spleen showed an occasional vessel with necrosis and organization. An old arterial lesion with necrosis, organization and marked thickening was found in the suprarenal gland. Several sections of the pancreas showed old healed lesions with thickening of vessels, some of which were thrombosed and recanalized. Old arterial lesions with thrombosis and recanalization were found in sections of the diaphragm. In the gallbladder were numerous typical necrotizing lesions, some showing healing (fig 4).

In summary, this patient had no evidence of rheumatic infection up to the time that scarlet fever developed eight weeks before admission. His symptoms may be classified into those definitely associated with rheumatic fever, namely, polyarthritis, fever, tachycardia, pallor and cough, and those which are unusual in this disease. We refer to the severe abdominal pains and cramps, and the pain in the scrotal region which developed about the same time. As the latter symptoms occurred practically simultaneously with those of the rheumatic polyarthritis and valvular lesions all within a period of a few weeks, one should expect to find that they were all part of the same disease. The abdominal symptoms might have been interpreted as part of the rheumatic disease (abdominal rheumatism), but such abdominal crises are also commonly observed among the symptoms of periaenteritis nodosa, and at autopsy organic changes were found to account for them in the vascular lesions within the abdomen. Finally, we wish to emphasize the acute rheumatic history with the rapid development of organic valvular change and the postmortem findings of typical acute rheumatic pancreatitis, including an acute auricular lesion and numerous Aschoff bodies in the myocardium.

CASE 2⁴—History—A V, admitted on Feb 27, 1931, was a schoolgirl, 10 years old. She had mild scarlet fever seven weeks before admission. Seven days later, urticaria appeared which lasted for four weeks and was accompanied by fever as high as 104.5 F. Migrating pains in the joints were associated with the febrile exacerbations. Examination of the urine on one occasion revealed a great deal of albumin. Three days before admission there were violent abdominal pain and rigidity, with tenderness especially marked over the upper quadrant on the right side. The blood count showed 14,000 leukocytes with 79 per cent polymorphonuclears.

Clinical Impression—The diagnosis was rheumatic fever with abdominal rheumatism. Because of the possibility of an intra-abdominal complication an exploratory operation was performed.

Findings at Operation—The appendix was normal, and except for distention of the intestines, some fine fibrinous exudate in the gastrohepatic ligament and edema around the duodenal tissues, no significant abnormalities were found. The foramen of Winslow was closed.

Course—Three days postoperatively bilateral bronchopneumonia developed. Shortly afterward a coarse pleural friction rub was heard, and there was marked tenderness over the whole lower part of the chest on the left side, with dulness on

4 This case is reported with the permission of Dr Murray H. Bass.

percussion During this period a distinct loud systolic murmur was discovered at the apex, varying in intensity and transmitted to the axilla, and occasionally transitory murmurs were heard at the base of the heart The temperature ranged between 100 and 103 to 104 F and the pulse rate from 120 to 140 The hemoglobin fell to 55 per cent, and the urine showed a heavy trace of albumin, many hyaline casts, leukocytes and occasional erythrocytes A blood culture was sterile A roentgenogram of the chest showed enlargement of the heart and pneumonic infiltration of the right base Later it was believed that there was a pericardial effusion Therapeutic measures were unavailing and the patient died on April 19, seven weeks after admission to the hospital



Fig 5 (case 2) —Verrucous endocarditis in a case of periarteritis nodosa Note the ridge of verrucae along the closure line of both leaflets of the mitral valve The small nodules at the center of each leaflet represent redundant valvular tissue

Autopsy—The diagnosis was periarteritis nodosa involving the kidney and the heart, acute rheumatic verrucous endocarditis of the mitral valve and the chordae tendineae, moderate hypertrophy of the left ventricle and dilatation of the right ventricle, old and recent adhesions of the pleura and peritoneum, petechial (purpuric) hemorrhages of the pericardium, pleura, kidney and peritoneum, minute infarcts(?) of the kidney, atelectasis of the lung and congestion of the viscera with hydrothorax and ascites

Gross Examination The right pleural cavity contained 400 cc of clear yellowish fluid There were easily separable adhesions between the pleura and the diaphragm on both sides, numerous petechial and purpuric spots on the visceral pleura and atelectasis at the bases of the lungs

The heart weighed 260 Gm. Seventy cubic centimeters of clear straw-colored fluid was found in the pericardium. The left ventricle was slightly hypertrophied and the right ventricle and right auricle were dilated. The mitral cusps were somewhat thickened and opaque, and the free edges showed a continuous row of fine verrucae (fig 5). At the middle of the closure line of the posterior leaflet was a smooth nodule the size of a millet seed. A somewhat polypoid formation measuring approximately 3 mm in diameter could be seen projecting from the closure line of the anterior leaflet at about its middle.

A moderate amount of clear yellow ascitic fluid was found in the peritoneal cavity. Numerous edematous thick adhesions were found in the right and left upper quadrants. The diaphragm on the right side was edematous and thickened. The liver weighed 890 Gm, was intensely yellow on section and showed indistinct lobular markings. The peritoneal coat of the gallbladder was thickened. Both kidneys were enlarged. There were lesions the size of split peas in the right kidney and one in the left—yellowish-white, triangular on section and localized to the cortex—which were probably infarcts. The pancreas showed marked congestion.

Microscopic Examination. In the heart were numerous young Aschoff bodies showing cells with basophilic protoplasm and ragged outlines, some with characteristic owl-eyed nuclei (fig 6). The mitral valve showed valvulitis with typical rheumatic verrucae. Two of the larger nodules seen grossly on the closure line represented redundant valvular tissue. One of the larger branches of the coronary artery showed a definite necrotizing lesion with destruction and fibrinoid degeneration of the media, thickening and fibrosis of the intima, destruction of the internal elastic layer and infiltration of the adventitia and periarterial region by round cells and granulation tissue. The lungs showed marked passive congestion. The arteries showed considerable sclerotic intimal thickening without inflammatory lesions. There was marked chronic passive congestion in the liver, with almost complete atrophy or destruction of the hepatic cells in the center of the lobules and lymphocytic infiltration of the portal spaces. The capsule showed fibrinous exudation with vascularized organization. Occasional necrotizing arteritis was evident in the kidneys (fig 7). The pancreas showed marked congestion with slight atrophy of the periphery of the lobules. In the aorta were local areas of swelling and necrosis of collagen fibers. In and about these areas there were prominent vasa vasorum which showed periarterial infiltration chiefly by round cells with few leukocytes. The infiltration was especially marked in the inner third of the adventitia and in some places involved the media as well. The gallbladder showed thickening of the serosa with organizing peritonitis. The diaphragm showed marked degeneration of the muscle fibers, and an organizing exudate was found on the peritoneal surface with marked thickening of the diaphragm.

In this case, as in the first, the onset of the illness was with an attack of scarlet fever. Polyarthritis with fever and albuminuria were present early. But these symptoms were associated with an attack of violent abdominal pain and abdominal rigidity which led to an operation, at which edema and fibrinous exudate were found around the duodenal tissues and gastrohepatic ligament, but with no purulent focus. Later there developed valvular disease of the heart, anemia, continued fever, pericarditis and enlargement of the heart. Again, as in the first case, there was a simultaneous association of rheumatic fever with abdominal

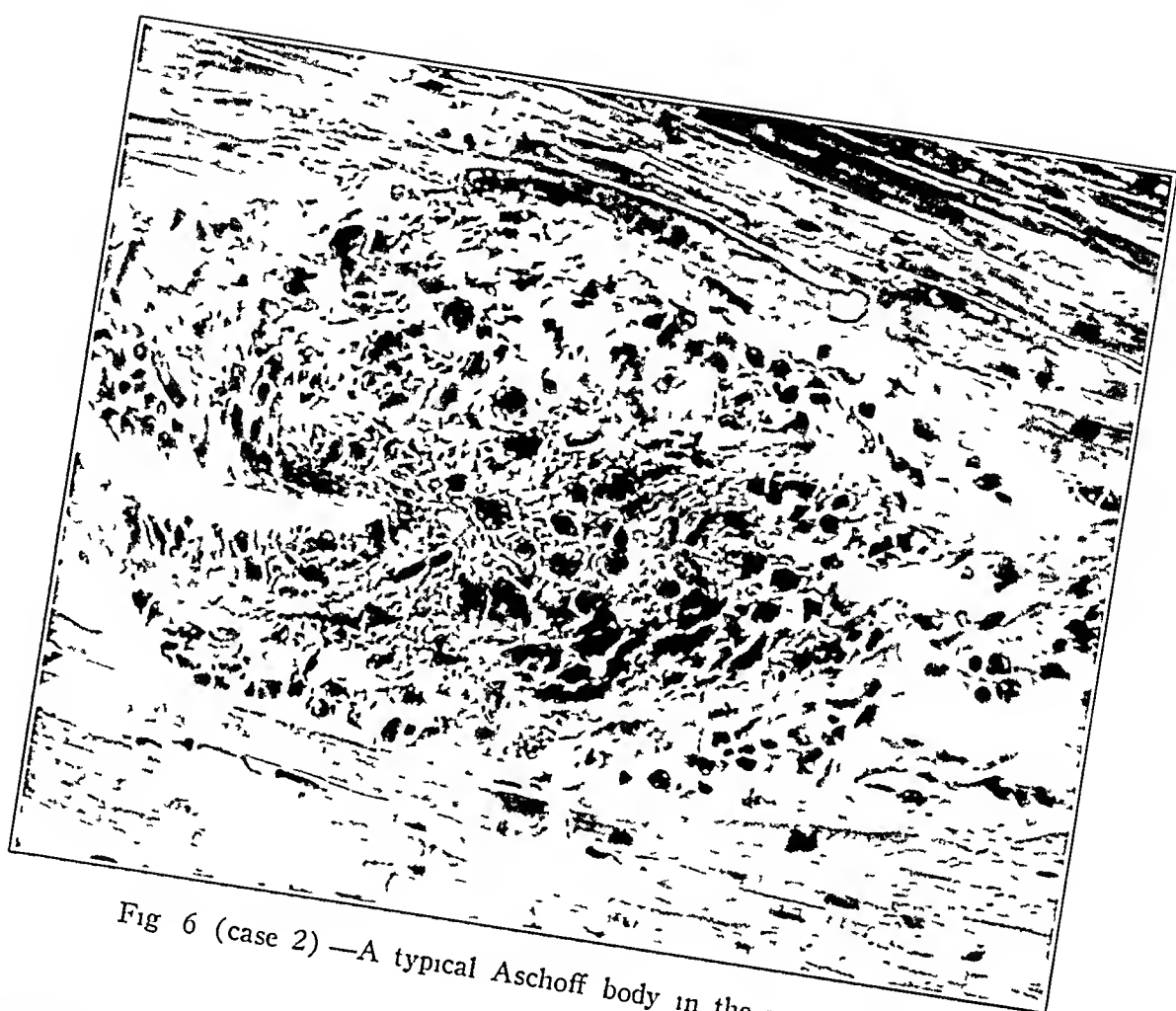


Fig 6 (case 2) —A typical Aschoff body in the myocardium

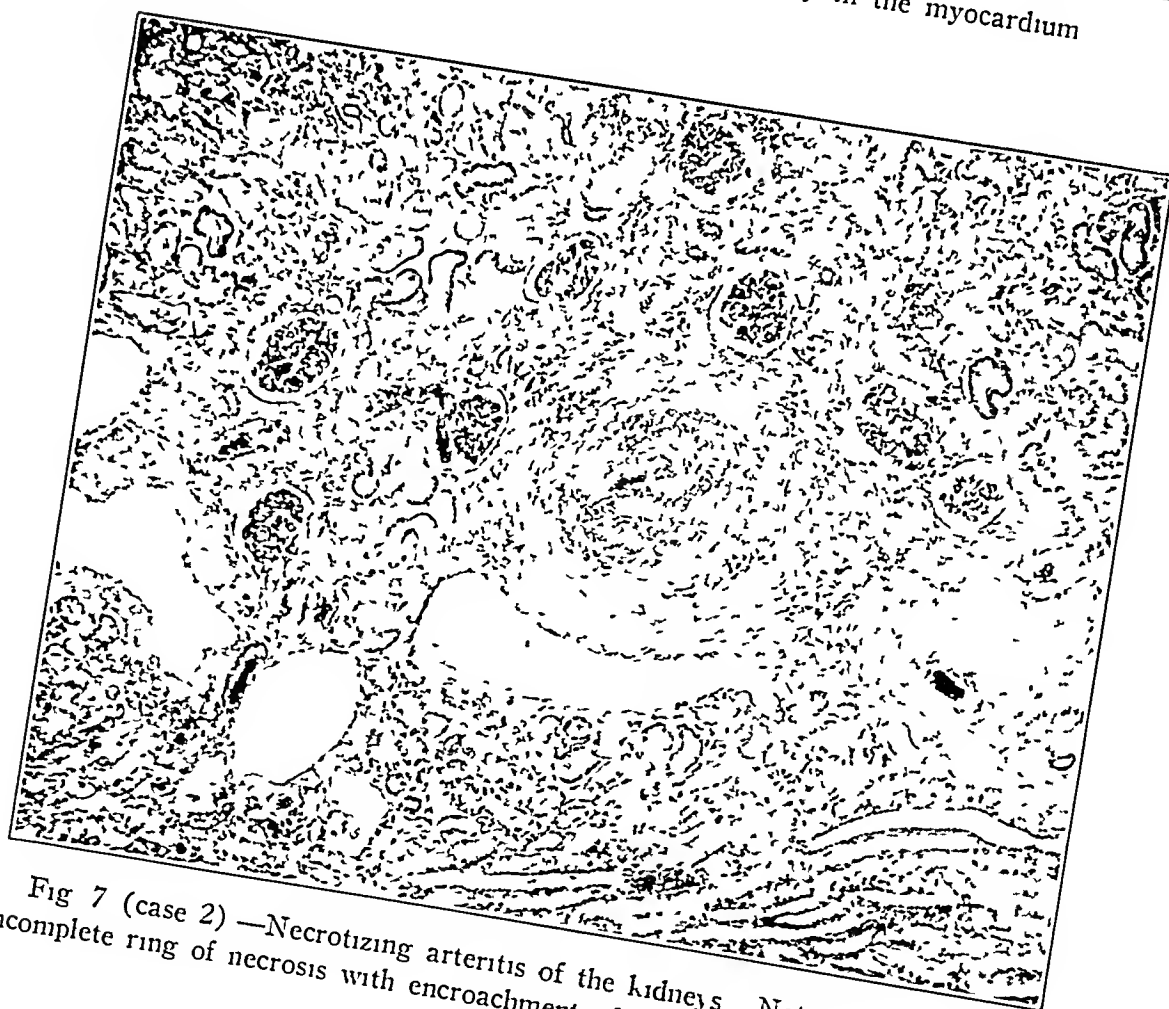


Fig 7 (case 2) —Necrotizing arteritis of the kidneys Note the characteristic incomplete ring of necrosis with encroachment of the intima on the lumen

symptoms, the latter so marked as to suggest an intra-abdominal complication, for which the operation was performed. Postmortem examination revealed verrucous endocarditis with fresh Aschoff bodies in the heart and typical peritonitis nodosa in the heart and kidneys.

CASE 3—History—A M., a man, aged 33, was admitted on March 11, 1931, with a complaint of fever and abdominal cramps for four weeks and migratory pains in the joints for two or three weeks. He had used alcohol to excess for six years. He gave a history of frequent sore throats and recurrent tonsillitis since childhood. He had gonorrhea twelve years before, with reinfection ten months before admission, but following active treatment had had no symptoms for eight months. The illness for which he was admitted began one month before with severe tonsillitis and cervical adenitis accompanied by chilliness and fever with the temperature at 103 F. The fever persisted for two or three days, and the patient was confined to bed for one week. On arising, pain in both knees required him to return to bed. Soon thereafter, pain and tenderness appeared in rapid succession in the elbows, ankles, shoulders and wrists and the metacarpophalangeal and clavicular joints. A purpuric rash appeared on the thighs. According to the patient, the joints of the ankles had been swollen, reddened and covered with a purpuric rash similar to that on the thighs. For two or three weeks persistent fever between 101 and 103 F., profuse sweats and recurrent arthritis had been present. In the past year he had had numerous attacks of distinct epigastric cramps, the last attack being followed by diarrhea associated with nausea and vomiting. The present abdominal symptoms were more severe than in previous attacks. Four days before admission there was an unusually dark stool, though not frankly tarry, followed by constipation for three days.

Examination—The patient was febrile and grunting with pain in the abdomen and in his joints. Examination of the heart revealed systolic murmur at the apex and over the left precordium. The second pulmonic sound was ringing and accentuated, and there was a suggestion of a pericardial friction rub. The abdomen showed rigidity, probably voluntary. There was tenderness in the hypogastrium with pain referred posteriorly to the lumbosacral region. The patient complained of extreme tenderness over the knees and right hip, with limitation of motion of these joints. There was a patellar click on both sides. On the flexor surfaces of the thighs was a purpuric macular rash, and a similar spray of macules was seen at the right lower costal margin posteriorly. The tourniquet test was positive.

Clinical Impression—The diagnosis was acute rheumatic fever with visceral manifestations, and ileus, either toxic or due to intestinal vascular thrombosis. Gonorrheal endocarditis was considered, and another suggestion was erythema with visceral manifestations (Osler's syndrome).

Course—The blood pressure was 145 systolic and 105 diastolic. The hemoglobin content was 86 per cent, and there were 17,000 leukocytes per cubic millimeter. A prostatic smear was negative for gonococci.

Abdominal symptoms now dominated the clinical picture. The surgeon's impression was that of peritonitis secondary to acute appendicitis. An exploratory operation gave essentially negative results. The appendix was removed. Then symptoms of acute nephritis and uremia appeared. At about this time the pathologic report on the appendix was that it showed multiple foci of necrotizing arteritis in all phases. In the next two months the temperature ranged between 101 and 103 F., the pulse rate between 100 and 120. There was increasing pallor, the hemoglobin

content being 47 per cent. Acute epididymo-orchitis developed. Four blood cultures were sterile. The Wassermann test of the blood and the gonococcic complement-fixation test were negative. Death from cardiac failure occurred on May 18.

Autopsy—The diagnosis was subacute periarteritis nodosa involving the heart, kidneys, gallbladder, pancreas, liver, lungs, diaphragm, stomach, intestines, bronchi and mesentery, rheumatic verrucous endocarditis, subacute fibrinous pericarditis, pericardial effusion, hypertrophy (moderate) of both ventricles, and productive meningo-encephalopathy.

Gross Examination The general appearance was one of marked emaciation and moderate pallor. There was a fading purpuric area on each heel. The parenchyma of the lungs showed closely packed minute pale nodules, smaller than miliary tubercles, and a few arteries filled with adherent pale red thrombi. Two hundred cubic centimeters of pericardial fluid was found, and a shaggy fibrinous exudate was present on the pericardium. There was nodular thickening of the coronary arteries. On the mitral valve small verrucae were scattered along the line of closure. The web of the leaflet was vascularized. The chordae tendineae were thickened. The diaphragm showed nodular thickening along the course of one of the larger arteries. In the liver irregular areas of hemorrhage were seen. Branched fibrous scars showed, on section, thickened obliterated arteries. Aneurysms and thromboses were seen in the left lobe. In the gallbladder, nodules the size of a pea along the course of the cystic artery were filled with blood clot. Also in the pancreas were a number of pea-sized aneurysms filled with blood clot. In the kidneys a number of tiny nodules were found in the course of the arcuate arteries and their branches, and there were hemorrhagic areas on the surface and in the pelvis (fig 8). Characteristic nodules were found along the course of many vessels of the gastro-intestinal tract. The right testis showed alternating areas of ischemia and congestion. In the brain there was thickening of the left vertebral artery near its junction with the right vertebral artery.

Microscopic Examination Several sections of the heart through the myocardium revealed typical interstitial rheumatic lesions, including young Aschoff bodies. In the epicardium were numerous typical arteritic lesions in the healing stage. A thick fibrinous pericardial exudate was found. The small and middle-sized arteries of the lungs showed acute necrotizing arteritis with cellular infiltration and occasional thrombosis. There was occasional evidence of hemorrhage with calcification.

The liver showed numerous arteritic lesions in the healing stage. There was complete closure of arterial lumens due to organized thrombi. An aneurysmal arteritic lesion with a recent complete thrombus was found in the pancreas, also healing arteritic lesions. Aneurysmal arterial lesions were found also in the suprarenal glands, as well as the fibrosing stage of arteritis. In the kidneys were many acute and chronic necrotizing and healing arteritic lesions with periarterial cellular infiltration, similar to those in the other organs. Some glomerular lesions resembled those of subacute diffuse glomerulonephritis of the intracapillary type. The testis showed necrotizing arteritis. Acute arteritic lesions were found in the submucosa and muscularis of the appendix (fig 9).

As in the preceding two cases, fever and polyarthritides were associated with abdominal pain. As in the second case, the abdominal pain dominated the clinical picture and led to an operation which yielded no adequate explanation of the symptoms until necrotizing arteritis was found in the appendix. The patient had a history of frequent sore



Fig 8 (case 3) —Necrotizing arteritis in the kidneys Note the hemorrhagic arteritis on the surface The cut section at the right shows thickened vessels and a large hemorrhage at the upper calyx

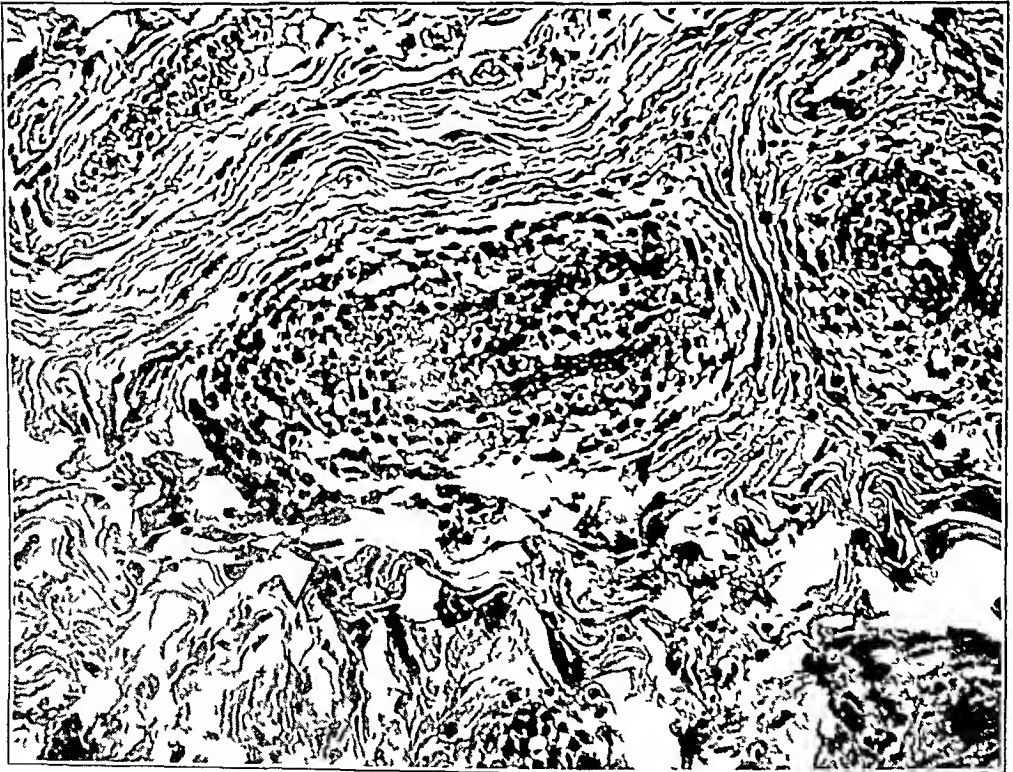


Fig 9 (case 3) —Necrotizing arteritis in the appendix Note the characteristic band of necrosis and periaarterial infiltration

throats and recurrent tonsillitis since childhood, and the present illness was initiated by an attack of severe tonsillitis. The clinical diagnoses of acute rheumatic fever with visceral manifestations and erythema with visceral manifestations (Osler's syndrome) were made at the first examination. Later there was a clinical picture of glomerulonephritis with uremia, and at the end cardiac symptoms dominated. Postmortem examination revealed widespread periarteritis nodosa in the active and healing stages. In this case the lesions were grossly visible, and there was present, in addition, the characteristic formation of aneurysms and thromboses which have been frequently described in this disease. It is conceivable that the greater number of healed lesions and the aneurysms were associated with the longer history of abdominal symptoms. Purpura associated with arthritic manifestations has been occasionally noted before⁵ in cases of periarteritis nodosa, and has sometimes led to the clinical diagnosis of Schonlein's purpura (peliosis rheumatica). Epididymo-orchitis has also been noted before, generally caused by necrotic lesions in the testicular arteries. Finally, we want to mention the involvement of the pulmonary vessels here as in the first case, as such an involvement has been noted only occasionally before.⁶ This case, therefore, presented classic evidence, both clinically and pathologically, of periarteritis nodosa simultaneously with clinical symptoms and pathologic confirmation of rheumatic pancarditis, including the presence of Aschoff bodies.

CASE 4—History—A S., a woman, aged 30, was admitted on Aug 6, 1933, with a complaint of headaches, weakness, nausea and vomiting for four weeks. An attack of rheumatic fever at 11 years of age lasted for three months and another attack at 16 lasted for one month. In the past few years the patient had noticed dyspnea on exertion, occasional precordial pain and palpitation. In the last six months nocturia (five or six times each night) had been present. Aside from these symptoms, she was fairly well until four weeks before admission when violent frontal and vertical headaches developed, with a blurring of vision, accompanied by occasional hematuria, moderate burning on urination, continuous nausea and vomiting. A new symptom was diffuse abdominal pain. In the preceding three days a slight cough developed, with blood-specked sputum and pain in the right side of the chest anteriorly. There had been occasional night sweats.

Examination—The blood pressure was 206 systolic and 146 diastolic. The breath had a urinous odor, and there were drowsiness, vomiting and twitching. The heart was enlarged, and there was a long blowing diastolic murmur to the left of the sternum, best heard at the apex. A gallop rhythm was evident at the apex. The second pulmonic and second aortic sounds were reduplicated, the former

5 (a) Zimmermann. Arch f Heilk 15 167, 1874. (b) Schreiber. Inaug Dissert., Königsberg, 1904, quoted by Gruber¹⁴. (c) Lamb. Periarteritis Nodosa. A Clinical and Pathological Review of the Disease, Arch Int Med 14 481 (Oct) 1914. (d) Frommel. Ann de méd 19 42, 1926. (e) Hutinel, Coste and Arnaudet. Arch de méd d enf 33 355, 1930.

6 Ophuls, W. Periarteritis Acuta Nodosa, Arch Int Med 32 870 (Dec) 1923.

being louder. The fundus oculi showed marked papillitis with destruction of the disk markings, the veins were engorged, and the optic disk was reddened. Urinalysis revealed marked albuminuria, a low specific gravity and many erythrocytes. The blood urea nitrogen was 115 mg per hundred cubic centimeters. The Wassermann test of the blood was negative, the hemoglobin content was 45 per cent.

Clinical Impression—The diagnosis was rheumatic cardiovalvular disease, mitral stenosis (?) and malignant sclerosis with uremia.

Course—Increasing signs of uremia developed with convulsions and pulmonary edema, and death occurred suddenly on August 8, three days after admission.

Autopsy—The diagnosis was periarteritis nodosa of the heart, iliac arteries, gallbladder, kidneys, intestines, liver, pancreas and bladder, malignant nephrosclerosis, marked hypertrophy of the left ventricle and slight hypertrophy of the right ventricle, pulmonary edema, hemorrhagic gastritis and ileitis, and bilateral chronic salpingitis.

Gross Examination—The heart weighed 700 Gm. There was marked hypertrophy of the left ventricle, and the mitral valve flaps were thickened and their edges rounded. There was fusion of the right posterior commissure with bridging of the aortic valve. A yellowish-white, firm nodule was found on the serosal surface of the gallbladder. On section this nodule had a lumen and was in close proximity to an artery. The surface of the kidneys was granular and pale red, with scattered, elevated areas of hemorrhage the size of a pinhead. Irregular grayish-white areas were found in the cortex, which was somewhat narrow. The medulla was congested and had areas of hemorrhage. The interlobular arteries were visibly thickened, and their narrowed lumens gaped widely on the cut section. There were grayish nodules on the serosal surface of the ileum.

Microscopic Examination—The endocardium of the left auricle showed an acute lesion with swelling and necrosis of collagen and cellular infiltration (fig 10). The mitral valve was thickened, there was swelling and necrosis of its substance, marked capillarization and infiltration by round cells and a few polymorphonuclear cells. On the anterior cusp of the mitral valve, near the closure line, was an early verrucous hyaline deposit. The aortic valve showed somewhat similar changes with collagen swelling, fibrinoid degeneration, infiltration by cells and vascularization of both the valve and the ring. The tricuspid valve showed similar but less marked changes. The myocardium contained focal areas of cellular infiltration and near the ventricular endocardium an occasional Aschoff body, including the characteristic multinucleated cells.

In the kidneys some glomeruli had tufts adherent to the capsule, and others were entirely hyalinized. The most marked alterations were in the vessels. Both the larger interlobular branches and the smaller arteries and arterioles were involved in a necrotizing arteritis. There was occlusion of many vessels by thromboses and organization. The stomach revealed moderate vascular alterations, and the vessels of the intestines showed intimal proliferation with encroachment on the lumen. The entire wall of the gallbladder was thickened, all coats being involved, especially the serosa. The vessels showed the characteristic necrotizing infiltrative changes already described (fig 11). There were thickened vessels in the portal spaces of the liver, and the little vessels in the interlobular spaces of the pancreas had thickened walls with small lumens. The urinary bladder showed typical arterial lesions.

The patient had recurrent attacks of rheumatic fever between the ages of 11 and 16 years. Her present symptoms of four weeks' duration

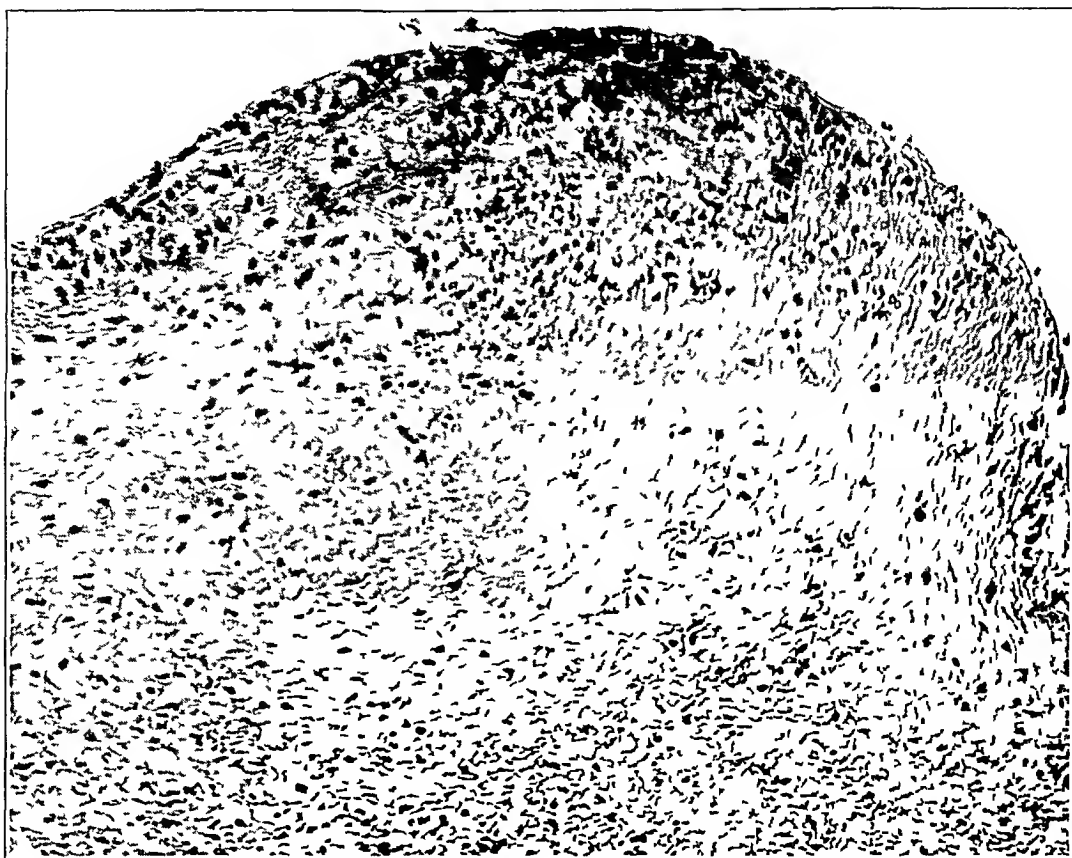


Fig 10 (case 4) —The endocardium of the left auricle showing acute inflammation with swelling and necrosis of collagen and cellular infiltration

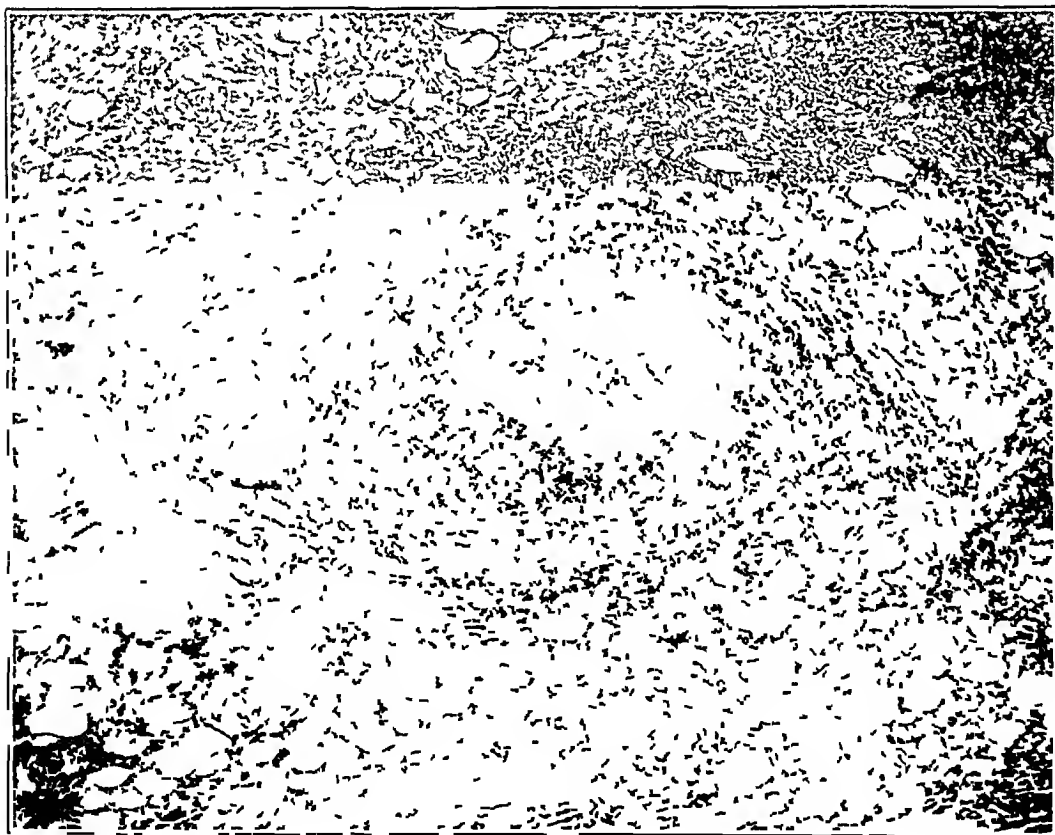


Fig 11 (case 4) —Necrotizing arteritis of the gallbladder There is severe necrosis with loss of boundaries between the various arterial layers, and marked arterial and periarterial inflammation

were those of uremia. She had, in addition, nocturia, albuminuria and hematuria. Because of the rapid course of the disease, the severe hypertension, the hematuria and the neuroretinitis the patient was considered clinically to present typical malignant nephrosclerosis. In addition there was diffuse abdominal pain, the origin of which was not clear. Examination of the heart pointed to rheumatic mitral stenosis, a diagnosis which was supported by the history of rheumatic fever, but this element in the case was neglected in view of the dominating picture of uremia. Postmortem examination showed widespread typical periarteritis nodosa, although macroscopically this could be suspected only from the presence of a single large nodule on the cystic artery. As in the other cases presented, the abdominal pain was a significant and confusing symptom. Despite the presence of this and the renal symptoms, the clinical picture of malignant sclerosis was too clearcut to allow any suspicion of the presence of periarteritis nodosa.

A definite history of rheumatic fever, together with physical signs of mitral stenosis, was present in this case, but there was no attack, as far as could be determined, immediately preceding the patient's admission to the hospital. However, postmortem examination revealed, in addition to old thickening and vascularization of the valves, an acute rheumatic auricular lesion and occasional typical Aschoff bodies.

The postmortem findings in the kidney included such vascular lesions as are ordinarily found in periarteritis nodosa, as well as those alterations (extreme vascular narrowing) which confirmed the clinical diagnosis of malignant sclerosis.

COMMENT

Before discussing the significance of the not infrequent association of acute rheumatic fever with periarteritis nodosa as demonstrated in our cases, brief mention should be made of the criteria employed for the diagnosis of these conditions. For the purposes of this report we have assumed that the presence in the myocardium of typical Aschoff bodies was essential for the diagnosis of rheumatic heart disease. At the same time we must emphasize that in each of the cases reported there was, in addition, a history of febrile polyarthritis, in three this occurred during the final hospitalization. In the fourth case there had been at least two definite attacks of rheumatic fever between the ages of 11 and 16 years requiring rest in bed for from one to three months each time. Furthermore, in each case there were physical signs which indicated the presence of rheumatic heart disease. Finally, at postmortem examination there were not only Aschoff bodies but other evidences of rheumatic carditis, such as acute auricular lesions, inflammation and vascularization of the valves, collagen necrosis, fibrinous pericarditis and characteristic rheumatic verrucous vegetations on the

valves We have not been able to accept such isolated and less common pathologic findings as were utilized recently by Rossle and by Klinge and his co-workers for the diagnosis of rheumatic disease Had we been less strict in our criteria, we might have included at least three other cases of periarteritis nodosa associated with rheumatic heart disease

Even though it is likely that periarteritis nodosa is not a specific disease, but results from the activity of many toxic or infectious agents, there are, nevertheless, certain features which clearly distinguish it—features not present in those isolated instances of arteritis described by Wiesel,⁷ Wiesner,⁸ Siegmund⁹ and others in scarlet fever, diphtheria, typhoid fever, influenza, pyemia and other forms of chronic bacterial infections The descriptive basis for the diagnosis of periarteritis nodosa has been presented in detail in the protocols Briefly, this has consisted, on the one hand, of an alterative degenerative process in the media, sometimes including the intima, sometimes all three coats, leading to a characteristic ringlike band of necrobiotic tissue including degenerated muscle cells and fragmented elastica In addition, there has been arteritis, most marked in the media and adventitia, including periarterial infiltrations, frequently with evidences of healing as indicated by the invasion of the area by granulation and fibrous tissue

Periarteritis nodosa has a fairly definite though protean clinical picture, on the basis of which Redlich,¹⁰ Stepp,¹¹ Beer,¹² Sacki¹³ and others have been able to make the diagnosis during life even without biopsy As can be seen from Gruber's¹⁴ review of cases up to 1926 and from more recent reports, the same clinical features are present in the great majority of the patients These consist, in brief, of a febrile illness (in about 90 per cent) resembling a chronic general infection (sepsis) but with negative blood cultures, renal symptoms resembling nephritis, acute abdominal symptoms simulating an acute intra-abdominal complication or those of enterocolitis, and polyneuritis or polymyositis simulating pains of rheumatic fever From this it can be seen that the failure to make an accurate diagnosis *intra vitam* is due

7 Wiesel *Wien klin Wchnschr* **19** 723, 1906, *Med Klin* **19** 163 and 197, 1923

8 Wiesner *Wien klin Wchnschr* **19** 725, 1906

9 Siegmund *Centralbl f allg Path u path Anat* **35** 276, 1924

10 Redlich, quoted by Silbermann *Monatschr f Psychiat u Neurol* **2** 225, 1929

11 Stepp *Deutsche med Wchnschr* **56** 437, 1930

12 In an unpublished case in our series

13 Sacki *Med Klin* **20** 44, 1924

14 Gruber *Zentralbl f Herz- u Gefässkr* **18** 145, 165, 185, 205, 226, 245 and 269, 1926

not to the inadequacy or indefiniteness of the symptoms but to the variety of common diseases which periarteritis nodosa can simulate because of its extensive pathologic processes. In two of the cases reported here the symptoms suggested the presence of intra-abdominal complications and were followed by exploratory operations which gave negative results. The local arterial lesions described in various infectious diseases rarely constituted the basis of clinical symptoms.

Not only does periarteritis nodosa, in the majority of cases, manifest itself clinically in a fairly characteristic manner, but there are also pathologic alterations distinguishable from those in other infections. The disease is not characterized merely by the presence of a destructive and inflammatory vascular lesion, although this is fundamental. The cases we have presented, as well as those previously reported, indicate that the vascular lesions are scattered throughout the body and involve almost invariably the heart and kidneys and generally the liver and the gastro-intestinal tract. Furthermore, within any given organ or section of an organ the vascular involvement is most extensive, including the main arteries as well as the finer arterial branches. Generally (in our cases, three of four), though not invariably, there is macroscopic visibility of the lesions in the organ either in the form of nodules (aneurysms) along the arterial course or at least in the form of streaks made by the extensively thickened vessels.

These points are mentioned as a basis for contrast with the changes in other diseases to be described later in which occasionally an analogous lesion was present. But in these other diseases the lesions involved at most one or two organs in any given case, implicated only the finest arterial branches, were never macroscopically visible and generally gave no clinical symptoms. We exclude, of course, mycotic aneurysms in general infections and aneurysms due to syphilis, because in these instances a specific causative organism is available and the lesions are readily distinguishable microscopically. It is significant that in the cases we have seen, as well as in the extensive material previously reported, the microscopic lesions of periarteritis nodosa as observed in biopsy specimens, whether taken from subcutaneous nodules or from an organ removed at operation, have been sufficiently characteristic when considered with the clinical features of the disease to permit a correct diagnosis as confirmed by later postmortem examination.

On the basis of the strictest criteria for rheumatic heart disease and of the characteristics generally acceptable for the diagnosis of periarteritis nodosa we have reported four cases in each of which these diseases were associated. On the basis of other evidence, a relationship between these two diseases has been repeatedly conjectured before. We wish to review this evidence briefly.

Clinically, both conditions suggest infectious diseases with a rather prolonged febrile, "septic" course, yet with persistently negative blood cultures. In both, arthritic symptoms, cutaneous manifestations including subcutaneous nodules, anemia and tachycardia present superficial resemblances. Experimental attempts (Siegmund,⁹ Klinge¹⁵ and Metz¹⁶) to produce in animals the tissue changes of rheumatic fever or periarteritis nodosa have gained results which, according to the experimenters, resembled both diseases. In both instances one is dealing with a disease of unknown etiology. Both have been considered by definite groups of investigators to be the expression of an allergic reaction in a person sensitized to more than one agent rather than the result of infection by one specific organism. Strong support for the allergic theory has been found in the observation that both diseases are frequently preceded by one of a large number of bacterial infections or specific infectious diseases.

Ophuls,⁶ Gruber¹⁴ and others have listed rheumatic fever among a large group of infectious diseases in the previous history of patients with periarteritis nodosa. However, of the cases now available in the literature (almost two hundred) we have been able to discover only sixteen¹⁷ with a preceding history of arthritis or rheumatic fever. It is difficult to determine whether these were cases of rheumatic infection in the stricter sense in which we employ the term. It must be remembered that a considerable percentage of patients with periarteritis nodosa suffer from polymyositis, and that undoubtedly some of the patients with so-called pains in the joints were really suffering from muscular disease. Other cases with vague arthritic pains without associated fever were probably instances of infectious or rheumatoid arthritis rather than of acute rheumatic fever. This belief is substantiated by the fact that in individual reports of cases, at least as given in the literature, there is no mention of cardiovascular disease clinically or of postmortem evidence of rheumatic endocarditis, myocarditis or valvular deformity. The presence of rheumatic purpura (peliosis rheumatica or

15 Klinge. Beitr. z. path. Anat. u. z. allg. Path. **83** 185, 1929.

16 Metz. Beitr. z. path. Anat. u. z. allg. Path. **88** 17, 1931.

17 (a) Gruber. Virchows Arch. f. path. Anat. **258** 441, 1925. (b) Benedict. Ztschr. f. klin. Med. **64** 405, 1907. (c) Baló. Virchows Arch. f. path. Anat. **272** 478, 1929, cases 1, 2 and 9. (d) Blum. Wien. klin. Wchnschr. **42** 40, 1929. (e) Bock. Ztschr. f. Augenh. **69** 225, 1930. (f) Erlandsson. Acta psychiat. et neurol. **6** 369, 1931. (g) Herrenschild. Klin. Monatsbl. f. Augenh. **83** 419, 1929. (h) Carling and Hicks. Lancet **1** 1001 (May 19) 1923. (i) Longcope. Bull. Ayer Clin. Lab. Pennsylvania Hosp. **5** 1 (Dec.) 1908. (j) Stengel. Deutsches Arch. f. klin. Med. **167** 1, 1930. (k) von Spindler. Med. Klin. **20**: 1466, 1924. (l) Rosenblath. Ztschr. f. klin. Med. **33** 547, 1897. (m) van Paasen. Nederl. tijdschr. v. geneesk. **73** 4020, 1929. Schrieber^{5b} Hutinel^{5c}.

Schonlein's disease), as in the cases of Zimmermann,^{5a} Schreiber,^{5b} Lamb,^{5c} Frommel^{5d} and Hutinel and his co-workers,^{5e} in which the purpura (rather common in periarteritis nodosa) was associated with arthralgias, can in no way be interpreted as an attack of rheumatic fever. Of these cases only Lamb's was marked by clinical or pathologic evidence of cardiac involvement.

There are, however, reports of six cases in addition to those named in which endocarditis was found at postmortem examination. None of the authors of these reports mentioned Aschoff bodies or offered any other evidence to substantiate the rheumatic nature of the lesions. Motta¹⁸ found chronic endocarditis of the mitral valve and acute endocarditis of the aortic valve. No history is given, and no microscopic observations are mentioned. Lewis'²⁰ case was not associated with a history or clinical evidence of rheumatic infection, but the author spoke of mural endocarditis found at postmortem examination.

In the other four cases there is considerable though not conclusive evidence to indicate that periarteritis nodosa was truly associated with rheumatic disease. Benda's²⁰ patient (case 2) had had rheumatic fever with valvular disease clinically and showed chronic and recurrent endocarditis of the mitral and aortic valves at postmortem examination. Lowenberg's²¹ patient had a rheumatic history, systolic and diastolic cardiac murmurs and, at autopsy, chronic fibrous endocarditis of the aortic valve. Janssen's²² patient had a history of both scarlet fever and rheumatism and clinical evidence of aortic stenosis and insufficiency, and postmortem examination revealed recurrent verrucous endocarditis with scarring of the aortic valve. Neither of these reports gave microscopic descriptions. Lamb's first patient^{5c} had acute polyarthritis with a macular and purpuric eruption. In addition there was a pericardial rub. The clinical diagnosis was Schonlein's disease. At postmortem examination there were an acute inflammatory exudate on the pericardium and an endocarditis of the mitral and pulmonary valves. Microscopically the vegetation was described as consisting of organizing thrombus with cocci on the surface, but there were no other microscopic cardiac findings suggesting rheumatic fever. It must be clear that these cases cannot be accepted as conclusive for the presence of rheumatic disease any more than the three cases of ours mentioned earlier which are not included in this report. It should be remembered, however, that none of these writers were investigating their cases from the point of view of

18 Motta Ann Fac de med de São Paulo 4 99, 1929

19 Lewis Proc Path Soc Philadelphia 14 134, 1911-1912

20 Benda Berl klin Wchnschr 45 353, 1908

21 Lowenberg Med Klin 19 207, 1923

22 Janssen, P Ztschr f urol Chir 10 130, 1922

rheumatic fever, and that study from this point of view might have revealed more conclusive proof

A few cases described in the literature as cases of sepsis may well have been instances of periarteritis nodosa associated with rheumatic fever. Case 1 of Klinger²³ and case 4 of Semsroth and Koch²⁴ are examples of this. More pertinent is the case of Strang and Semsroth¹ (also reported as case 2 of Semsroth and Koch) presented as an instance of vascular lesions in *Streptococcus viridans* septicemia. The illustrations and descriptions are highly suggestive of periarteritis nodosa. In this case Aschoff bodies were found in the myocardium. The verrucous vegetations appear to have been those of a rheumatic rather than those of a bacterial endocarditis. The only positive blood culture was one made just before death, but such positive cultures may occasionally be encountered in rheumatic fever (Lichtman and Gross²⁵).

Another argument for the relationship of periarteritis nodosa to rheumatic fever has been seen in the discovery of arterial lesions in rheumatic disease. Since Bouillaud's²⁶ classic treatise in 1840, the association of arterial disease with rheumatic fever has been mentioned by numerous French writers. Except in the cases of Hanot²⁷ and Leger,²⁸ this association was based purely on clinical grounds, and in the reports of those writers microscopic descriptions are not available. In 1904²⁹ and again in 1906,³⁰ in his discussion of Lupke's presentation of periarteritis nodosa among stags, Aschoff mentioned that occasionally in rheumatic endocarditis there were nodular thickenings on the smallest branches of the coronary arteries due to circumscribed periarterial inflammatory changes with medial destruction. These reminded him of periarteritis nodosa. Geipel, in 1907,³¹ also spoke of changes in rheumatic heart disease resembling periarteritis nodosa, and described two instances of a destructive process involving the anterior descending coronary artery and on one vessel a suggestion of a beginning aneurysm. He could not determine whether vessels in other parts of the body were similarly affected. Whatever destructive elements were present in these vessels he ascribed to the mechanical pressure from rheumatic nodules.

23 Klinger. *Frankfurt Ztschr f Path* **42**: 455, 1931-1932

24 Semsroth, K, and Koch, R. *Krankheitsforschung* **8** 191, 1930

25 Lichtman and Gross. *Streptococci in the Blood in Rheumatic Fever, Rheumatoid Fever and Other Diseases*, *Arch Int Med* **49**:1078 (June) 1932

26 Bouillaud, J. B. *Traité clinique du rhumatisme articulaire*, Paris, J. B. Baillière, 1840

27 Hanot. *Presse méd* **1**:171, 1894

28 Leger, H. *Thèse de Paris*, no 267, 1877

29 Aschoff. *Verhandl d deutsch path Gesellsch* **18** 46, 1904

30 Aschoff. *Verhandl d deutsch path Gesellsch* **10** 157, 1906

31 Geipel. *Munchen med Wchnschr* **54** 1057, 1907

In 1909³² he described seven cases of rheumatism, in two of which there were destructive changes in the smaller vessels with secondary intimal growth due to the pressure of Aschoff bodies. At the same time, in a description of vascular lesions in rheumatism, Coombs³³ mentioned the smallest branches of the coronary arteries as being the seat of nodular periarteritis.

The nonsyphilitic aneurysms discovered in cases of rheumatic fever have been sometimes interpreted as showing a significant similarity to the aneurysms frequently present in periarteritis nodosa. In such cases, if postmortem findings and satisfactory bacteriologic studies are not present, one must consider the possibility of the mycotic origin of the aneurysms, and interpret the condition as bacterial endocarditis complicating rheumatic heart disease. Siegmund³⁴ found mycotic aneurysm in 21 per cent of cases of "sepsis lenta." Klotz' case (1913)³⁵ with aneurysm of the ascending aorta may be of this type. We have already mentioned Geipel's report³¹ in which there was a suggestion of an aneurysm of a coronary artery. The diagnoses of Renon³⁶ and of Bezançon and Weil³⁷ were made on roentgen examination, and no pathologic report is available.

The first really detailed description of arterial changes in rheumatic fever was made by Klotz³⁸ in 1912. These changes rarely affected the main coronary arteries, generally involving the finer ramifications. Further, these alterations were only slightly destructive, being mostly those of productive inflammation.

Very suggestive is the case of recurrent rheumatic fever described by Watjen³⁹ in which there was panarteritis with destructive changes involving the smaller coronary branches in the myocardium. He spoke of the lesion as arteritis nodosa rheumatica but reserved opinion as to its relation to periarteritis nodosa. The only pathologic changes were in the heart. An added point of interest in this case was the infiltration of the subpericardial region by eosinophils, as extensive eosinophilic infiltrations have been described in periarteritis nodosa.

The arterial lesions thus far described in rheumatic fever have generally involved a single organ, usually the heart or the aorta. More

32 Geipel. *Munchen med Wchnschr* **56** 2469, 1909.

33 Coombs. *Quart J Med* **2** 22, 1908, *Brit M J* **1** 620, 1911.

34 Siegmund. *Munchen med Wchnschr* **72** 639, 1925.

35 Klotz. *J Path & Bact* **18** 259, 1913-1914.

36 Renon, Louis. *Conférences pratiques sur les maladies du coeur et des poumons*, Paris, Masson & Cie, 1906.

37 Bezançon and Weil. *Ann de méd* **19** 175, 1926.

38 Klotz. *Tr A Am Physicians* **27** 181, 1912.

39 Watjen. *Verhandl d deutsch path Gesellsch* **18** 223, 1921.

significant is the report of Von Glahn and Pappenheimer,⁴⁰ who, in forty-seven cases of rheumatic heart disease, found arterial involvement ten times in the various organs, including the lungs, kidneys, perirenal and perisuprarenal adipose tissue, ovaries, testes, pancreas, sigmoid flexure and cecum. The alterations described, however, differed from those in periarteritis nodosa in several important respects. In the first place, while the lesions were found in a variety of organs, in any one of these ten cases generally one and rarely two organs were involved. While vascular disease in isolated organs has been described as periarteritis nodosa, it would be most unusual to find such isolated involvement in ten successive cases. Study of the literature reveals that at least the heart and kidneys are almost invariably involved in every case of periarteritis nodosa. Second, the vessels involved in the cases described by Von Glahn and Pappenheimer were generally of much smaller caliber than those in periarteritis nodosa. Finally, while these authors described necrotizing inflammatory and reparative alterations in their cases, certain findings are described which we have never observed in periarteritis nodosa, whereas certain other findings like thromboses, infarctions and aneurysms, commonly present in periarteritis nodosa, were absent in these cases.

It is of course conceivable that the arterial changes which they described are earlier or less marked alterations but qualitatively similar to and of the same significance as those in periarteritis nodosa. But the authors themselves concluded "While it is possible that certain cases of rheumatic vascular disease may have been interpreted as periarteritis nodosa, there are, as has been pointed out, very clear cut differential features. The final decision as to whether these two somewhat similar conditions are related, must be reserved."

More recently Klinge and Vaubel⁴¹ presented two pictures of vascular changes in "rheumatism" (not in our strict sense of the term) which they considered difficult to distinguish from periarteritis nodosa. One showed involvement of a mediastinal artery and one of an artery in the aortic adventitia. Aside from differences in the actual appearance of the vessel from that of typical periarteritis nodosa (pointed out by the authors themselves), these and other vascular changes were found only in isolated instances after long search through considerable rheumatic material. No clinical symptoms resulted from these alterations. In a recent report, Rossle⁴² presented a case (case 5) which he termed one of periarteritis nodosa and which he included in his rheumatic series. We cannot accept this case as being definitely

40 Von Glahn and Pappenheimer. *Am J Path* **2** 235, 1926

41 Klinge and Vaubel. *Virchows Arch f path Anat* **281** 701, 1931

42 Rossle. *Virchows Arch f path Anat* **288** 780, 1933

one of rheumatic heart disease or one of periarteritis nodosa. He stated on the basis of his observations that there is an essential relationship between these diseases.

From the foregoing review it can be seen that the evidence for the association of rheumatic fever and periarteritis nodosa has hardly more than suggestive value. Aside from the four cases presented in this report, we have been unable to discover any others in which there was unquestionable rheumatic heart disease associated with periarteritis nodosa, according to the criteria we have already stated. From the frequency with which we have observed this association in our own cases, it seems highly probable that some or many of the cases of periarteritis nodosa previously reported might have been regarded as presenting rheumatic cardiac lesions had they been studied from this point of view. It is becoming increasingly evident that periarteritis nodosa is not a rare disease. It is being recognized with increasing frequency. With larger series of cases available for study by individual observers, evidence for the association of rheumatic fever in these cases may be discovered more readily.

It is not our purpose in this report to enter into a discussion of the etiology or nature of rheumatic fever and periarteritis nodosa. Until we know more about them, we cannot say the final word as to their relationship to each other. The high incidence of rheumatic heart disease in this small series of cases of periarteritis nodosa is significant, and also the simultaneity of their clinical manifestations. In three of the four cases the symptoms of the final illness were due both to an acute attack of rheumatism and to the lesions of periarteritis nodosa. In the fourth case there were no obvious evidences of active rheumatic infection. Nevertheless, an acute rheumatic lesion was found in the heart. One must conclude that in these cases we were not dealing with two unrelated diseases, but that the periarteritis nodosa was one of the manifestations of the rheumatic infection.

A point of special interest in two of our cases was an attack of scarlet fever within eight weeks preceding the final illness. This may, of course, have been a mere accident, considering that both patients were young children not far removed from the most common age for this disease. At the same time, because of the brief interval between the attack and the obvious development of rheumatic heart disease as well as periarteritis nodosa, it may well be conjectured whether scarlet fever did not stand in some etiologic relationship to these diseases. This occurrence is of special interest to those who believe in the streptococcic etiology of rheumatic fever as well as to those who argue that the latter disease is an allergic response in a sensitized person. This

association could also be employed to reason that not only the rheumatic fever but the periarteritis nodosa was intimately associated with the preceding infection by the scarlatinal organism

Another obscure but interesting association is that found in our fourth case, in which, in addition to the periarteritis, the clinical and pathologic features of malignant nephrosclerosis were added to those of rheumatic fever. Fahr⁴³ maintained that malignant sclerosis is the result of the activity of one or more of several toxic or infectious agents. In addition to lead and syphilis he named rheumatic fever as one of these etiologic agents. In five of his cases of malignant sclerosis there was a history of rheumatic fever. In two of them the renal disease directly followed rheumatic infection. In our case the rheumatic fever was a recurring affair which gave no obvious symptoms after the patient's sixteenth year except those due to a diminished cardiac reserve. The postmortem appearance of the heart, however, suggested that there was active infection up to the patient's death. A survey of cases of periarteritis nodosa thus far reported showed that a not infrequent cause of death was uremia. The patients of Sacki,¹³ Manges and Baehr⁴⁴ and Lamb^{5c} had albuminuric retinitis as well as evidences of uremia. Some of these patients gave a history of rheumatic arthritis or revealed endocarditis at postmortem examination. The data available do not permit a diagnosis as to the basis of uremia in these cases. The marked hypertension and albuminuric retinitis suggest the likelihood that some of these at least were cases of malignant sclerosis. In our series of fourteen cases of periarteritis nodosa it is probable that three patients died of uremia associated with malignant sclerosis. Thus far in only one of these three cases has definite rheumatic heart disease been found.

Certain observations in the cases we have presented we believe are of considerable practical importance. The abdominal and gastro-intestinal symptoms in periarteritis nodosa have frequently been given as fundamental manifestations of the disease. Ulcerations of the intestine following arterial necrosis and occlusion have often produced a diarrhea simulating ulcerative colitis and occasionally have produced the more dramatic features of general peritonitis due to acute intestinal perforation (Zimmermann,^{5a} Lorenz,⁴⁵ Versé,⁴⁶ Beitzke⁴⁷ and Meyer⁴⁸)

43 Fahr Arch f Dermat u Syph **130** 1, 1921

44 Manges and Baehr Am J M Sc **162** 162, 1921

45 Lorenz Ztschr f klin Med **18** 493, 1891

46 Versé Munchen med Wchnschr **52** 1809, 1905

47 Beitzke Berl klin Wchnschr **65** 1381, 1908

48 Meyer Berl klin Wchnschr **58** 473, 1921

In other instances abdominal colic without such acute perforations has given rise to the picture of an intra-abdominal complication, and in certain instances laparotomies have been performed (Schmidt, Lemke,⁴⁹ Ophuls,⁶ Lamb,⁵⁰ Manges and Baehr⁴¹ and Gruber^{17a}) Such symptoms though less well known are not uncommon also in rheumatic fever In some recent observations on this subject, Libman⁵⁰ divided the main clinical types of rheumatic fever into arthritic, pulmonary, so-called typhoidal and gastro-intestinal (or abdominal) He said, "abdominal symptoms occur frequently, the most important being pain, vomiting, diarrhea and distension A clinical picture of appendicitis may be encountered Diarrhea in one endemic has been found to occur as frequently as in one third of the cases I have seen two cases of rheumatic fever associated from the onset with ulcerative colitis"

As early as 1737 Boerhaave⁵¹ stated that besides the joints in rheumatic fever the disease invades "sometimes the brain, lungs and bowels" Garrod,⁵² Pribram,⁵³ Coombs,⁵⁴ Curschmann and Eckstein⁵⁵ and others have described cases of rheumatic fever simulating acute appendicitis Either the abdominal symptoms subsided spontaneously or, when operation was performed, the findings were essentially negative In all the four cases which we have reported, abdominal pain was a significant part of the clinical picture In the second and third cases the symptom was so marked that exploratory laparotomies were performed Examination of the appendix removed in one of the cases revealed a necrotizing arteritis

While in some cases of rheumatic fever with abdominal symptoms previously reported a veritable peritonitis was discovered, in most, as in our two patients operated on, there was no adequate visible lesion to account for the symptoms Various reasons have been given to explain the occurrence of these cases of "abdominal rheumatism" Generally the abdominal symptoms have been considered as referred pains from pleurisy with or without pneumonia, pericarditis and other thoracic rheumatic manifestations or as due to an intercurrent complication Libman⁵⁰ sug-

49 Lemke Virchows Arch f path Anat **240** 30, 1922

50 Libman Tr A Am Physicians **43** 188, 1928

51 Boerhaave, quoted by Paul Medicine **7** 388, 1928

52 Garrod, A E A Treatise on Rheumatism and Rheumatoid Arthritis, London, C Griffin & Co, 1890

53 Pribram, A, in Nothnagel, H Specielle Pathologie und Therapie, Vienna, Alfred Holder, 1899, vol 5, pt 2

54 Coombs, C Rheumatic Heart Disease, New York, William Wood & Company, 1924, p 234

55 Curschman, Hans, and Eckstein, Albert Rheumaprobleme, Leipzig, Georg Thieme, 1929, vol 1, p 21

gested a vascular origin of such pains when he stated that general pains in rheumatism might be due to arterial or venous inflammation. Because of the observations in our cases and because of the considerations on abdominal rheumatism and periarteritis nodosa just mentioned, we cannot escape the conclusion that at least in some cases of rheumatic fever the gastro-intestinal or abdominal symptoms have a definite organic basis in the pathologic alterations of periarteritis nodosa. This leaves open the question of the mechanism of the abdominal pain in the latter disease, about which there are various explanations. The significant point is that these symptoms occur frequently in periarteritis nodosa. A number of medical conditions, such as pneumonia, coronary thrombosis and others, have been reported which have been mistaken for an acute abdominal complication and in which an unnecessary operation has added to the danger of the disease. We should like to add to these diseases rheumatic fever associated with periarteritis nodosa. The possibility of periarteritis nodosa should be considered in any case of rheumatic fever or rheumatic heart disease associated with marked abdominal symptoms simulating an acute intra-abdominal complication.

SUMMARY

1 Four cases that came to autopsy are presented, in which widespread periarteritis nodosa was associated with rheumatic fever and rheumatic heart disease, the latter was confirmed by the presence of Aschoff bodies in the myocardium.

2 These four were discovered in a series of eight cases of periarteritis nodosa which came to autopsy in the course of two years. Prior to this period there were five additional cases which came to autopsy. Two of the five patients had a rheumatic history and evidence of rheumatic valvular disease. Verrucous endocarditis was disclosed in both cases at postmortem examination.

3 Criteria for the diagnosis of rheumatic infection and of periarteritis nodosa are discussed. On the basis of these criteria, none of the cases of periarteritis reported in the literature presented adequate evidence of rheumatic heart disease. Conversely, none of the vascular lesions described in rheumatic fever could be truly called periarteritis nodosa.

4 Because of the frequency of the association of these diseases in our cases and the simultaneous occurrence of the symptoms of each, we believe it probable that rheumatic fever is a common cause of the vascular lesions termed periarteritis nodosa.

5 In two of the cases an attack of scarlet fever occurred eight weeks before the symptoms of the other ailments became manifest. This point is briefly discussed.

6 In another case there was clinical and pathologic evidence of malignant sclerosis. This is mentioned in connection with Fahr's belief that rheumatic fever is one of the causes of malignant sclerosis.

7 In two of the cases the abdominal symptoms, so common in periarteritis nodosa, dominated the clinical picture sufficiently to lead to an exploratory operation. We suggest that when acute abdominal symptoms are present in a patient suffering from rheumatic fever, complicating periarteritis nodosa should be considered. This complication is offered as an organic basis for some of the instances of so-called abdominal rheumatism.

SOME CYTOLOGIC AND SEROLOGIC ASPECTS OF INFECTIOUS MONONUCLEOSIS

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H A LAWSON, M D

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PROVIDENCE, R I

Cytologic and serologic studies of the blood of persons with "glandular fever" have led to a renewed interest in the condition. The demonstration of the marked increase of mononuclear cells, which has caused the general use of the term infectious mononucleosis, and the recent discovery by Paul and Bunnell¹ of a high concentration of sheep cell agglutinins in the blood of patients with the disease indicate that it is quite different from most infectious processes. Its importance, however, as a subject of investigation is far greater than that of a mere hematologic curiosity for the following reasons. First, it is a rather common and benign condition, an accurate diagnosis of which allows prompt reassurance of the patient and a fairly accurate prognosis as to duration and morbidity. Second, the differential diagnosis from more serious conditions, especially lymphatic leukemia, is of great importance. Third, a solution of the problem involved in the causation of the mononucleosis, the development of sheep cell agglutinins in the blood stream and the relation between these conditions may have broad implications in the field of immunology.

In the present communication, after a brief consideration of the clinical picture based on a study of 28 sporadic cases of the disease, we shall take up the cytologic and serologic aspects. Whether or not the condition is a disease entity or merely an unusual reaction to an ordinary infection of the upper respiratory tract cannot be completely settled by a study of the literature, although the reports of various authors who have studied epidemics, as summarized by Guthrie,² incline one strongly to the former view. It has been noted, however, that the epidemics tend especially to affect children, and that these patients

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1 Paul, J R, and Bunnell, W W. *Am J M Sc* **183** 90, 1932

2 Guthrie, C C, in Christian, H A. *Oxford System of Medicine*, New York, Oxford University Press, 1927, vol 5, p 498

usually show a much less striking blood picture than is seen in sporadic cases in young adults. As far as we are aware, also, there have been no investigations as to the presence or absence of sheep cell agglutinins in the blood of patients during an epidemic. We must conclude, therefore, that the identity of the disease in the epidemic form and in sporadic cases such as are considered here is still to be proved.

CLINICAL AND CYTOLOGIC ASPECTS

By Drs BURGESS, LAWSON AND WELLMAN

Clinical Picture—Excellent descriptions of the clinical aspects of the disease are to be found in the literature.³ Our clinical observations agree in general with those reported in the literature. We have been impressed with the variation in the severity of the disease, as has been emphasized by Baldrige, Rohmer and Hansmann.^{3c} All gradations have been observed between a condition of marked prostration with a high fever (from 103 to 105 F) and such mild attacks that the patient stayed at his duties throughout most of the illness and had almost no fever. Enlargement of the lymph nodes, which is such a striking feature in most cases, may be relatively slight in a person in whom mononucleosis is excessive and the fever and prostration marked. Tenderness of the lymph nodes is, however, usually very definite. Enlargement of the spleen, usually appearing several days after the onset, has been noted in some cases, in 1 of which (case 26) tenderness of the spleen became marked and spontaneous pain in the left upper quadrant of the abdomen was present for twenty-four hours. Pain in the back of the neck on moving the head, due apparently to the tender nodes, has been a common and usually an early manifestation. Headache has been frequent, and sore throat has usually been present, but not always prominent. A marked, harassing cough, facial edema and swelling of the eyelids were noted in 2 instances. Jaundice, which was reported in 1 case by Mackey and Wakefield,⁴ was present in 2 of our patients. In 1, a physician of 40 years, who was prostrated by the disease, the jaundice was fairly intense. In this instance the blood gave a direct biphasic reaction to the van den Bergh test, suggesting toxic or infectious hepatitis rather than obstruction. The quantitative reading was 8 van den Bergh units, and the icteric index was 50. Pharyngeal ulceration

3 (a) Sprunt, T. P., and Evans, F. A. *Bull. Johns Hopkins Hosp.* **31**: 410, 1920. (b) Downey, H., and McKinlay, C. A. *Acute Lymphadenitis Compared with Acute Lymphatic Leukemia*, *Arch. Int. Med.* **32**: 82 (July) 1923. (c) Baldrige, C. W., Rohmer, T. J., and Hansmann, G. H. *Glandular Fever (Infectious Mononucleosis)*, *ibid.* **38**: 413 (Oct.) 1926. (d) Longcope, W. T. *Am. J. M. Sc.* **164**: 781, 1922.

4 Mackey, R. D., and Wakefield, A. M. *Ann. Clin. Med.* **4**: 727, 1926.

and exudation were frequently seen, and the organisms of Vincent's angina were present in the blood smears in some instances and absent in others. With 1 exception, a child of 6 years, the patients were all young adults, most of them students or teachers, and the sexes were about equally divided. In a few patients the mild secondary anemia referred to by Fitz-Hugh⁵ was noted. All recovered completely after a duration of febrile illness varying from under one to over five weeks.

Cytologic Changes in the Blood—In studying the appearance and character of the mononucleosis our greatest interest has been in the proper classification of the so-called abnormal forms which make up a large proportion of the mononuclear cells at the height of the disease. In examining fixed smears stained by Wright's method, all gradations have been noted between normal lymphocytes, small and large, and the medium and large "abnormal" cells with vacuolated or deep blue cytoplasm. These cells have been well described by Downey^{3b} and by Baldrige and his associates^{3c}. Their most striking characteristics are the vacuolated cytoplasm, often with little irregular projections from the surface of the cell, and the nuclei with coarse chromatic masses varying in shape from round to irregular or deeply cleft. Frequently cells with very deep blue cytoplasm are seen. The commoner forms of abnormal cells are shown in figure 1 A.

In certain of these abnormal forms a somewhat lighter, more uniform cytoplasm and a few azure granules appear, in other words, they tend more to resemble the normal adult lymphocyte. In 1 case (27) the predominating cell in a blood smear taken fairly early in the disease was a medium or large lymphocyte in which azure granules were numerous, but a day or two later the more deeply staining forms without azure granules replaced them. In some cases from small to medium-sized lymphocytes predominate, which in the deep staining of their cytoplasm and the irregular shape of their nuclei resemble the large "abnormal" cells. It is probable, from morphologic studies of the abnormal cells in fixed smears, that these cells are lymphocytes. If so, they must be, according to Sabin⁶ and Wiseman,⁷ immature forms, and those with the deep blue cytoplasm very young forms. In some cases the more adult lymphocytes with azure granules are rare, and the predominating cell is one of varying size but with a deeply basophilic cytoplasm.

If, then, one considers the abnormal forms as immature lymphocytes and remembers that the absolute lymphocyte count reaches a high

5 Fitz-Hugh, T, Jr, in Piersol, G M. Encyclopedia of Medicine, Philadelphia, F A Davis Company, 1932, vol 6, p 709.

6 Sabin, F R. Bull Johns Hopkins Hosp **34**:277, 1923.

7 Wiseman, B K. J Exper Med **54** 271, 1931.

figure in many cases, it seems probable that there is such a strong stimulus to multiplication of lymphocytes in this disease that young forms of an unusual type are seen. This impression is heightened by the occurrence of binucleated forms. In lymphatic leukemia similar abnormal lymphocytes and occasionally binucleated forms are seen. Figure 1 *B* is a camera lucida drawing of two cells, the upper one from a case of lymphatic leukemia and the lower one from a case of infectious mononucleosis. Figure 1 *C* is a similar drawing of a cell, in what appears to be the last stage of cell division, from another patient with mononucleosis. These observations suggest that in infectious mononucleosis, as in lymphatic leukemia, amitosis of lymphocytes may occur in the circulating blood. This has been described by Hall⁸ in the blood of normal monkeys (*Macacus rhesus*), but never in human beings, so far as we know, except in leukemia.

The idea that the abnormal cells are lymphocytes is further strengthened by the use of the supravital staining technic reported by Wilson and Cunningham⁹. We applied this method in 1 of our cases with similar results. Most of the cells showed large neutral red vacuoles and mitochondria that were large, numerous and irregularly distributed. Thus the available data make it clear that in this disease there is a strong stimulus to cell division in the germinal centers of the lymph nodes and spleen resulting in a marked absolute increase of lymphocytes, mature, immature and abnormal, in the circulating blood.¹⁰

SEROLOGIC ASPECTS

By C. A. STUART

Sheep Cell Agglutinins in Blood Serums from Normal Persons—The presence of agglutinins for sheep erythrocytes in the human blood stream until recently has been a subject primarily of academic interest

8 Hall, B. E. *Folia haemat* 38 30, 1929

9 Wilson, P., and Cunningham, S. *Folia haemat* 38 14, 1929

10 During the period in which the lymphocytosis is noted there is an absolute diminution in the number of granulocytes which show a decided shift to the left, the proportion of stab cells to the segmented forms being as high as 7:1 in some instances. This has been mentioned by various observers (Pepper, O. H. P., and Farley, D. L. *Practical Hematological Diagnosis*, Philadelphia, W. B. Saunders Company, 1933, p. 429; Fitz-Hugh, T., Jr., in discussion of Mullin, W. V., and Large, G. C. *Filament-Nonfilament Count*, *J. A. M. A.* 97 1138 (Oct 17) 1931; Piney, A. *Recent Advances in Hematology*, Philadelphia, P. Blakiston's Son & Co., 1927, p. 121). In the case reports of Rosenthal and Wenkebach (*Klin. Wchnschr.* 12 449, 1933) this fact is also noted, and it is of interest that in the cases which they reported as resembling mononucleosis clinically but as giving negative results serologically this shift to the left was missing.

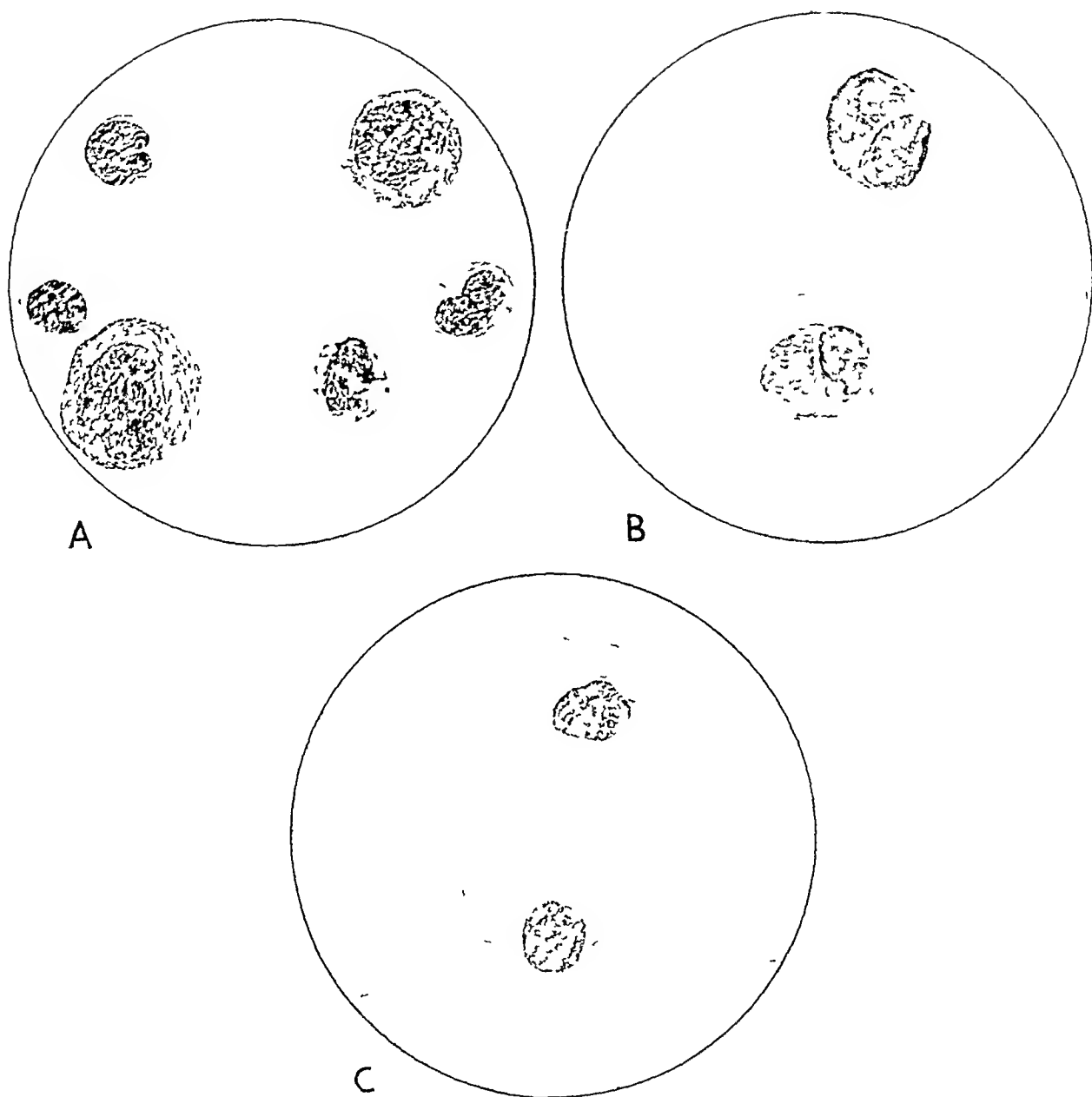


Fig 1 — *A*, a composite field showing types of lymphocytes commonly found in infectious mononucleosis. The cells at the upper left and right center represent the most common type of abnormal lymphocytes. The cells at the lower left and upper right are large forms with deep basophilia. The cell at the left center is a normal adult lymphocyte, for comparison. The cell at the lower right with basophil granules is thought by some observers to represent degenerating forms. *B*, a composite field showing binucleated forms. The upper cell is from a patient with acute lymphatic leukemia, the lower cell, from a patient with infectious mononucleosis. *C* a lymphocyte, apparently in the final stage of amitosis.

The work of Davidsohn¹¹ and of Paul and Bunnell,¹ however, who found that under certain pathologic conditions the concentration of sheep cell agglutinins in human beings was significantly increased, necessitates a clear understanding of not only the presence but also the concentration of these antibodies in normal human serum. Investigators agree that these agglutinins are present in some normal human serums, but unfortunately there is considerable disagreement as to the percentage of human beings possessing these antibodies and as to the concentration of the antibodies in the serum when present. As an example of the extreme divergence in the findings of the various investigators the work of Deicher¹² and Kagan¹³ may be cited. The former reported that most of the human serums that he examined did not possess agglutinins specific for sheep cells and that in the few cases in which they were present

TABLE 1—*Comparison of the Titers for Sheep Cell Agglutinins in Normal Serums, from the Reports of Various Investigators*

Deicher ¹²		Davidsohn ¹¹		Bunnell ¹⁴		Stuart, Burgess, Lawson and Wellman		Kagan ¹³	
Dilu tions	Per Cent Positive	Dilu tions	Per Cent Positive	Dilu tions	Per Cent Positive	Dilu tions	Per Cent Positive	Dilu tions	Per Cent Positive
Negative	Most	Negative	7	Negative	40.7	Negative	0.00	Negative	0.00
1:4	Few	1:3.5	20			1:5	3.00		
		1:7	24	1:8	23.3	1:10	23.00	1:7	0.00
		1:14	30	1:16	22.2	1:20	46.33	1:14	8.55
		1:28	18	1:32	9.0	1:40	20.66	1:28	20.29
		1:56	1	1:64	4.0	1:80	6.00	1:56	23.39
				1:128	0.8	1:160	0.66	1:112*	30.43
						1:320	0.33	1:224	11.59
								1:448	1.45
								1:896	4.34

* For convenience the dilutions 1:112 and 1:140 have been combined in the dilution 1:112.

the antibodies could be demonstrated only in a dilution of 1:2. On the other hand, Kagan¹³ maintained that in all serums he tested these antibodies could be demonstrated in dilutions ranging from 1:10 to 1:640. While not confirming Deicher's results some investigators are inclined to think that his conclusions are more nearly correct than those of Kagan, others tend to favor the conclusions of Kagan. Thus there seems to be general disagreement as to the concentration of sheep cell agglutinins in normal human serum.

In the course of our investigations in infectious mononucleosis, serum from 300 normal persons or from persons with pathologic conditions other than infectious mononucleosis has been examined for the concentration of sheep cell agglutinins. Generally speaking our titers are

11 Davidsohn, I. J. Infect. Dis. **53**:219, 1933.

12 Deicher, H. Ztschr. f. Hyg. u. Infektionskr. **106**:561, 1926.

13 Kagan, N. W. Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:20, 1931.

lower than Kagan's,¹³ but higher than those of Bunnell¹⁴ The latter's findings, however, are higher than Davidsohn's, whose titers, in turn, are higher than those of Deicher¹² These differences are shown in table 1, in which the findings of these investigators are tabulated according to the final dilution (to be discussed later) of serum in the test In the practical application of the increase in sheep cell agglutinins to pathologic conditions interest should be centered not so much on the percentage of normal serums possessing agglutinins or on the average titer of the normal serums (normal only with respect to serum disease and infectious mononucleosis), as on the height to which the titer may rise in such serums For this reason the actual number of serums examined is of little significance, since if the work is accurately done the finding of 1 normal serum with a high titer in 100 cases is statistically more significant than finding no serum with a high titer in 1,000 cases The discrepancies in the reports of the investigations tabulated are so great that obviously one must look for some variation other than that in the individual serums examined to explain the discrepancy

A careful review of the literature convinces one that many if not all of the discrepancies can be traced to wide differences in the technique employed in making and recording the results of the tests Kagan¹³ in testing a serum in a 1:10 dilution used 0.25 cc of the dilution in question, to which he added 0.1 cc of the cell suspension The final dilution of serum was then 1:14 Bunnell,¹⁴ on the other hand, used 0.5 cc of the 1:10 dilution of the serum, to which he added 0.5 cc of the cell suspension with 1 cc of saline solution, making the final dilution of the serum 1:40 Yet both reported their results in terms of a 1:10 dilution This fact alone will account for some of the confusion in the reports of investigators It is to be regretted that the failure to report results in terms of the final dilution of serum is so common, because in reviewing the work of different men it is usually necessary to reduce all dilutions to the final dilution of the serum This procedure is often laborious and sometimes impossible, since all the facts are not given, in which case comparison is not possible For this reason abstracts dealing with dilutions of serum, particularly those involving low titers, in which technical details are omitted, are often misleading All this confusion would be eliminated if investigators would report their work in terms of final dilution

Deicher¹² used 1 cc of a specified dilution of serum, with 1 cc of a 5 per cent cell suspension He used, then, a final concentration of cells of 2.5 per cent, whereas practically all other investigators used a final concentration of approximately 0.5 per cent In order to determine the effect of varying cell concentrations in this reaction the following experi-

14 Bunnell, W W *Am J M Sc* 186 346, 1933

ment was tried. From a single normal human serum, in quantities of 0.5 cc., four sets of serial dilutions ranging from 1:2.5 to 1:1,280 were prepared in serologic tubes, 100 by 10 mm. To the first set of tubes was added 0.5 cc. of a 5 per cent suspension of sheep cells, giving a final cell suspension of 2.5 per cent and final serum dilutions of from 1:5 to 1:2,560. To the three remaining sets of tubes was added 0.5 cc. of cells of such concentration that the final cell suspensions were 0.5 per cent, 0.1 per cent and 0.02 per cent, respectively. All the tubes were shaken and incubated at 37.5 C. for two hours. Deicher¹² made his final reading at the end of two hours of incubation, while all other investigators seem to have recorded their results after the tubes had

TABLE 2—*Sheep Cell Agglutination in Serums of Twenty-Five Normal Human Beings with Varying Concentrations of Sheep Cells After Two Hours at 37.5 C.*

	Dilutions									
	Negative	1:5	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280
2.50 per cent cells	24	1								
0.50 per cent cells	24			1						
0.10 per cent cells	17	4	1	2		1				
0.02 per cent cells	6	5	6	6	1			1		
The Same Tests After an Additional Twelve Hours at 5 C.										
2.50 per cent cells	10	11	4							
0.50 per cent cells		1	9	12						
0.10 per cent cells					11	11	2	1		
0.02 per cent cells						1	8	11	4	1
The Same Tests After an Additional Two Hours at 37.5 C.										
2.50 per cent cells	23	2								
0.50 per cent cells	23	1			1					
0.10 per cent cells	13	1	6	3	1	1				
0.02 per cent cells	1	3	10	8	1	1		1		

remained in the icebox overnight. We, therefore, noted the degree of agglutination after two hours at 37.5 C., placed the tubes in the icebox at approximately 5 C. and made a second reading twelve hours later.

In table 2 are tabulated the results of the first reading on 25 separate experiments. The figures opposite the cell concentration give the number of serums that were positive under the dilution specified. Thus, when a 2.5 per cent cell suspension was used, 24 of the 25 serums were negative and 1 was positive in a dilution of 1:5. These results are in perfect accord with those of Deicher¹². With a cell concentration of 0.5 per cent, 24 serums showed no agglutination and 1 serum agglutinated in a 1:20 dilution. As the concentration of the cell suspension decreased, however, agglutination did occur in some of the serums. In the 0.02 suspension 6 serums were negative and 1 serum (the one that agglutinated in the other concentrations) agglutinated in a dilution of 1:320. Quite different results were obtained when the tests were read after twelve hours at 5 C. One hundred per cent of the serums

were positive in the 0.5 per cent suspension in dilutions ranging from 1:5 to 1:80, while in the 0.02 per cent suspension 100 per cent of the serums were positive in dilutions ranging from 1:80 to 1:1,280.

It is evident from table 2 that the concentration of sheep cells used in the test and the temperature at which the tests are incubated exert a profound influence on agglutination. Experience has shown that individual variation in packing sheep cells to prepare suspensions for the test, such as the size of the centrifuge tube used, the proportion of cells to saline solution, the total volume in the tube and particularly the speed and time used in centrifugation, may give a difference in the final reading of titers from 1 to 2 dilutions. We have not investigated the effects of temperature other than to note that a difference might arise from variations of temperature in the icebox. It was noted, however, that tests in which the results were read after twelve hours at 5°C and the tubes then replaced in the icebox for another twelve hours invariably gave a somewhat higher titer, from one to two dilutions, at the end of the twenty-four hours. Whether this is due to the continued slow adsorption of agglutinins throughout the twenty-four hours or to more efficient adsorption because of thoroughly shaking the tubes at the end of twelve hours, we cannot say.

As soon as the difference in the readings on tubes placed in the incubator and in the icebox was noted the possibility of cold agglutinins seemed likely, and the tubes were again incubated at 37.5°C for two hours and the titers again noted. (Landsteiner,¹⁵ working on the agglutinins in human serum for homologous cells, found one agglutinin flocculating cells only at low temperature. This agglutinin, which was found to be separate from other agglutinins in human serum and serologically specific for its homologous antigen, he called a "cold agglutinin.") The results of the final readings are recorded in table 2. The titers obtained from serums placed in the icebox are almost completely reversible, since reheating the tubes disperses the agglutinated cells and lowers the titers to practically the same level that was found after the first two hours of incubation at 37.5°C. One serum, however, agglutinated the 0.5 per cent cell suspension in a 1:20 dilution after two hours at 37.5°C and in a 1:40 dilution after twelve hours at 5°C, and dropped back only 1 dilution, to 1:20, after being reheated for two hours in the incubator. In addition to the 25 specimens of serum just mentioned 96 others were examined for reversibility, using only the regular 0.5 per cent cell concentration. In this number only 3 irreversible serums were found. It is interesting to note that reversibility is not dependent on the height of the icebox titer since in the serums examined, 2 having an icebox titer of 1:160, 7 with a titer of 1:80 and 17 with a titer of

15 Landsteiner, K., and Levine, P. J. *Immunol* 12:441, 1926.

1 40 were completely reversible, while the 3 serums which were irreversible possessed icebox titers of 1 20, 1 40 and 1 80. Two hours at 37.5 C is by no means essential for complete reversibility since some serums having icebox titers of 1 40 or 1 80 were completely reversed in from ten to thirty minutes at room temperature. Individual serums after agglutination in the icebox seem to differ in the speed of reversion.

The question naturally arises as to whether in this case one is concerned with cold agglutinins, pseudo-agglutinins or merely better agglutination at low temperature. That pseudo-agglutination can be definitely ruled out will be seen from the following experiment. One cubic centimeter of a 1 2 dilution of each of the aforementioned 96 serums was adsorbed with 0.5 cc of packed sheep cells for two hours at 5 C with frequent shaking. The cold tubes were centrifugated for two minutes, after which the supernatant fluid was removed as rapidly as possible. Twenty-five-hundredths cubic centimeter of the supernatant fluid was placed in each of 3 tubes. To the first tube was added 0.25 cc of a 1 per cent sheep cell suspension and to the second the same amount of a 0.04 per cent cell suspension, while to the third tube was added 0.25 cc of a 1 per cent suspension of rabbit cells. The tubes were kept at 5 C for twelve hours. Of the 96 serums tested in this way none showed any agglutination with the 0.5 per cent concentration of sheep cells and only 1 serum reacted positively with the 0.02 per cent concentration. All 96 serums completely agglutinated the rabbit cells. Furthermore, several serums were adsorbed for two hours at 5 C, placed in the incubator at 37.5 C for two hours and then centrifugated, after which the supernatant fluid was tested for sheep cell agglutinins. Agglutinins were found in all the supernatant fluids, though in varying concentrations. (Jervell,¹⁶ working with human iso-agglutinins, reported similar findings.) Obviously, then, agglutination of sheep cells by human serums at low temperature is a specific antigen-antibody complex, and the agglutinins which are adsorbed at low temperature are in part at least released at high temperatures. Whether or not we are dealing with a specific cold agglutinin of the type described by Landsteiner¹⁷ is a problem beyond the scope of this paper.

It has been shown that the agglutinating titer of normal human serums for sheep erythrocytes may be greatly influenced by the concentration of cells, the temperature at which the tests are incubated and the length of incubation. Furthermore, it is the practice of some technicians, on removing serum from the icebox after overnight incubation, to let the tubes stand at room temperature or even in the incubator for varying lengths of time before the tests are read, until the

16 Jervell, M. *J Immunol* 6:445, 1921.

17 Rosenthal, N., and Wenkebach, G. *Klin Wchnschr* 12:499, 1933.

moisture which collects on the tubes has been dispelled. Such a procedure greatly alters the reading, depending of course on the time elapsing between removal from the icebox and reading of the tests. It should also be borne in mind that reading hemagglutination tests employing a 0.5 per cent concentration of cells is not as simple as reading bacteriologic agglutination tests. In the latter case a single flirt of the tube is often sufficient to read the test, but in the former, in which pseudo-agglutination is often pronounced in tubes containing an appreciable amount of serum, the tubes must be flirited several times in order to get a true reading. All these things serve to emphasize the fact that the test must be carefully standardized before it can be successfully used in routine work.

Sheep Cell Agglutinins in Serums from Persons with Infectious Mononucleosis—The serums from 14 persons in whom the clinical and cytologic pictures were in every way consistent with the diagnosis of

TABLE 3—*Titer of Sheep Cell Agglutinins in the Serums of Patients with Infectious Mononucleosis*

Case	Titer	Case	Titer	Case	Titer
15	1 1,280	20	1 2,560	25	1 5,120
16	1 640	21	1 610	26	1 2,560
17	1 1,280	22	1 1,280	27	1 1,280
18	1 320	23	1 610	28	1 5,120
19	1 640	24	1 640		

infectious mononucleosis were examined. The titers of these serums, which ranged from a dilution of 1 320 to one of 1 5,120, will be found in table 3. The findings unquestionably support the contention of Paul and Bunnell¹ that the test is a valuable aid in the diagnosis of infectious mononucleosis. Yet no report on this subject has sufficiently emphasized the fact that the agglutination test unsupported by the clinical and cytologic evidence may result in a false diagnosis. Rosenthal and Wenkebach¹⁷ are inclined to believe that a titer as low as 1 64 (final dilution) is indicative of infectious mononucleosis, irrespective of the cytologic picture. Bunnell,¹⁴ however, found that 4.8 per cent of 1,600 Wassermann serums had a titer of at least 1 64. Of 300 normal and Wassermann serums examined by us, 6.99 per cent had titers of at least 1 64. To call such a high percentage even of Wassermann serums positive for infectious mononucleosis is obviously impossible. Bunnell found a differential of only a single dilution between his normal specimen with the highest titer (1 126) and his positive serums with the lowest titer (1 256). Excluding the 1 serum having a titer of 1 320 (to be discussed later), there is a similar differential of a single dilution from 1 160 to 1 320. Any serologic test with such a low differential between the negative and positive serums can hardly

be expected to inspire the clinician or the technician with confidence. Serologic interest, then, should center on those cases in which the clinical, cytologic and serologic picture is doubtful, rather than on the high titer in acute conditions which can be diagnosed without the aid of the agglutination test.

The agglutinations at icebox temperature which occurred in all the normal serums were reversible in approximately 97 per cent of the cases. It seemed that this fact could be utilized in the test, since in no case in which the clinical and cytologic pictures were definitely those of mononucleosis was irreversibility in the agglutination found even when the tubes were reincubated at 37.5 C for several hours. Among the serums tested for mononucleosis before irreversibility was noted were 3 in which the clinical, cytologic and serologic findings were doubtful. The 3 serums, A, B and C, at 5 C gave sheep cell titers of 1:160, 1:160 and 1:320, respectively. Reexamined for reversibility five months after the original examination, A still showed a titer of 1:160 at low temperature, but was completely reversible at 37.5 C; B, one month subsequent to the first test showed a titer of 1:160 at 5 C, but was likewise reversible at 37.5 C. Serum C, examined several times over a period of eight months, constantly agglutinated sheep cells in a dilution of 1:320 at 5 C, but only to 1:80 at 37.5 C. The complete reversibility of agglutination in the first 2 serums and the low titer of C at 37.5 C, together with the length of time over which the agglutinins persisted in the blood of the latter, led us to conclude that these three doubtful cases were negative with respect to infectious mononucleosis.

It is highly probable that the test for sheep cell agglutinins in the serum of patients with a condition suggestive of mononucleosis will soon become a routine procedure. In view of the findings we propose certain changes in the technic advocated by Paul and Bunnell¹. These investigators used 0.5 cc of the serum dilution, 0.5 cc of a 2 per cent sheep cell suspension and 1 cc of saline solution. The total volume of 2 cc results in such a column of liquid in the usual 100 by 10 mm tubes that a satisfactory reading can be made by only placing the finger over the end of the tube and tilting it 3 or 4 times. In routine work there is a certain element of danger in this method since in the same rack a technician may have agglutination tests for pathogenic organisms, and it is not improbable that on occasions the wrong tube may be inverted with the finger over the end. The extra 1 cc of saline solution plays no rôle in the test and should be omitted. The same concentration of cells can be obtained by adding 0.5 cc of a 1 per cent suspension. In order to insure uniform sheep cell suspensions for the test, all suspensions should be prepared from 2 cc of concentrated washed cells which have been centrifugated in 8 cc of saline solution for five minutes at a speed of approximately 2,200 revolutions a minute. A final

reading should be made after four hours of incubation at 37.5 C, since incubation for two hours at this temperature is not sufficient to give complete agglutination in any dilution, regardless of the final titer. If this is not convenient the tests, as soon as completed, may be put in the icebox overnight to be read the next morning after incubation for two hours at 37.5 C, with occasional shaking. In this way the often confusing cold agglutination is dispersed, making the diagnosis far more certain. We are of the opinion that a serum which agglutinates sheep cells by this procedure in a dilution of 1:80 may be classed as suggestive. But it should be remembered that the agglutinins do not appear in the blood stream in any significant concentration until several days after the first appearance of symptoms, therefore a suggestive serum should not be made the basis of a negative diagnosis until further tests have been made. With substantiating clinical and cytologic pictures serums agglutinating in dilutions of 1:320 or more may well be considered positive.

Nature of the Sheep Cell Agglutinins in Mononucleosis—Davidsohn¹¹ expressed the opinion that the increase in the agglutinin content in the blood in serum sickness is specific for sheep erythrocytes, and on the basis of adsorption tests concluded that the antibody is heterophile. Kagan,¹³ on the other hand, concluded that the increase in agglutinins was nonspecific since the titers for rabbit cells were increased to practically the same extent. Our serums which were positive for mononucleosis were tested for rabbit as well as sheep cell agglutinins. The results are in accord with Davidsohn's¹¹ in that, while there is a slight rise in all cases in the rabbit cell agglutinins, the increase is insignificant in comparison with the increase in the sheep cell titer. Two cases that were carefully studied in this respect, with titers examined weekly for several weeks after the onset of symptoms, will serve to illustrate the point. In the first case the sheep cell titer rose from no agglutination in a dilution of 1:5 at 37.5 C to 1:5,120, whereas the rabbit cell titer increased from 1:80 to 1:160. In the second case the sheep cell titer rose from negative to 1:2,560, while the rabbit agglutinins increased from 1:160 to 1:1,280.

Investigators¹⁸ consistently referred to the sheep agglutinins in mononucleosis as heterophile antibodies, without attempting to justify their statement other than by adsorption with raw sheep cells. Three of our positive serums with the highest titer (cases 26, 27 and 28) were successively adsorbed 3 times in a dilution of 1:25 with raw and boiled sheep erythrocytes and emulsions of guinea-pig kidney, guinea-pig testicle and rabbit kidney. As a control over nonspecific adsorption, a specially activated charcoal was also used. The results of the adsorp-

18 Paul and Bunnell¹ Bunnell¹⁴ Rosenthal and Wenkelach¹⁷

tion tests will be found in table 4. Sheep cell agglutinins in such serums are readily adsorbed with both raw and boiled sheep cells and, as might be anticipated, they are not removed to any appreciable extent by rabbit erythrocytes or emulsions of rabbit kidney. It is surprising, however, that emulsions of guinea-pig kidney and testicle which carry the heterophile antigen were not more effective in removing the agglutinins. On three other occasions such serums were repeatedly adsorbed with various emulsions of guinea-pig tissues, including a suspension of connective tissue, but the results were practically the same. Attention is called to the unusual degree of nonspecific adsorption obtained with the charcoal.

TABLE 4—*Adsorption of the Sheep Cell Agglutinins in Mononucleosis Serum with Various Substances*

Materials Used for Adsorption	Serum Adsorbed	First Adsorption	Second Adsorption	Third Adsorption
Raw sheep cells	25	—	—	—
	26	—	—	—
	28	—	—	—
Boiled sheep cells	25	+	—	—
	26	—	—	—
	28	++	—	—
Raw rabbit cells	25	+++	+++	+++
	26	+++	+++	++
	28	+++	+++	+++
Guinea pig kidney	25	+++	++	—
	26	+++	+	—
	28	+++	+++	+
Guinea pig testicle	25	+++	++	+
	26	++	+	—
	28	+++	+++	++
Rabbit kidney	25	+++	+++	++
	26	+++	++	+
	28	+++	+++	+++
Norite charcoal	25	++	—	—
	26	+	—	—
	28	+++	+	—

Before the heterophile nature of the sheep cell agglutinins in the blood stream of patients with infectious mononucleosis can be unreservedly accepted one curious fact must be explained. Schiff and Adelsberger¹⁹ and numerous others have shown that in man heterophile antigen is present in the cells of groups A and AB. Kraitschewsky,²⁰ however, expressed the opinion that heterophile antigen is present to some extent in the cells of all four groups. In nine of our positive cases the blood was typed, 2 were in group O, 2 in group B and 5 in group A. One patient in group A had a sheep cell titer of 1:5,120 for both agglutinins and hemolysins. How, then, is the presence of these two

19 Schiff, F, and Adelsberger, L. *Ztschr f Immunitätsforsch u exper Therap* 40:334, 1924

20 Kraitschewsky, I. L., and Messik, R. E. *Ztschr f Immunitätsforsch u exper Therap* 56:130, 1928

incompatible substances, heterophile antigen in the erythrocytes and antibody in the serum coexisting in the same blood stream without any apparent reaction, to be explained? There appear to be no symptoms in infectious mononucleosis consistent with those that might be anticipated from such an interaction

Serum containing heterophile antibodies is toxic for the guinea-pig whose tissues contain heterophile antigen. Therefore, 0.5 cc of the serum of 2 patients with mononucleosis having titers of 1:640 and 1:1,280, respectively, for sheep cell agglutinins was injected intravenously into guinea-pigs weighing 300 Gm. The same amount of serum from normal persons and serum from a rabbit immunized against guinea-pig kidney, which possesses heterophile antigen, was injected into similar animals as controls. Mild anaphylactic symptoms were noted in the animals into which the serums from patients with mononucleosis and from normal human beings were injected. The injection of rabbit anti-kidney serum, however, resulted in typical anaphylactic death in from five to ten minutes. It is possible that an insufficient amount of mononucleosis serum was injected into the guinea-pigs (more serum could not be obtained), yet the rabbit anti-kidney serum which was fatal possessed an agglutinating titer for sheep cells of only 1:160. On the other hand, 1 patient (case 26), with a previous history of sensitivity to horse serum, reacted markedly to a test dose of horse serum, which carries the heterophile antigen. If the antibodies in mononucleosis are heterophile, and it must be assumed that they are until more evidence to the contrary is produced, the clinician must bear this in mind should the use of therapeutic horse serum for any reason seem advisable during the course of the disease.

REPORT OF CASE

CASE 26—S. A., a woman, aged 26, was a graduate student. The onset of the condition was on Oct. 30, 1933, after a cough for three or four days. The chief complaints were fever, swollen eyelids and a severe hacking cough. There was little or no headache. The patient was first seen on October 31. The temperature was 100 F and the pulse rate 98. The eyelids were swollen, and an enlarged and tender lymph node was evident below the angle of the jaw on the right side, with one or two slightly enlarged and tender lymph nodes in the posterior cervical area on the right side. There was a small patch of exudate on the right tonsil.

November 1. The distressing cough and the swelling of the eyelids continued.

November 2. Slightly enlarged and definitely tender lymph nodes were evident in the posterior cervical region on the left side. The axillary nodes were enlarged, but not tender. The spleen was not palpable. There was no enlargement of the inguinal nodes.

November 3. The spleen was palpable. Prostration was fairly marked.

November 4 The spleen had increased in size and was tender The inguinal nodes were definitely enlarged but not tender

November 8 The spleen was still larger and more tender There was spontaneous pain in the region of the spleen during the night

November 13 The spleen was barely palpable and slightly tender The cervical nodes were smaller and not tender, the inguinal glands were still enlarged but not tender A test dose of horse serum was injected intradermally into the left forearm There was a marked local reaction including a wheal 2 cm in diameter and an area of redness 13 cm in diameter (still discernible at the end of a week) There was a blotchy redness from the shoulder to the wrist

November 21 The patient was apparently well

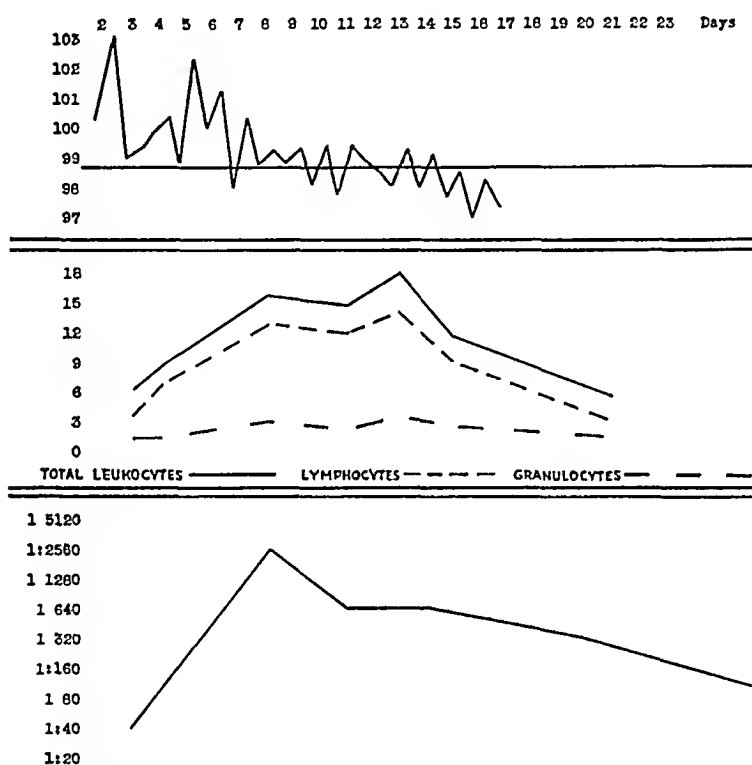


Fig 2 (case 26) —Record of patient with marked sensitivity to horse serum upper section, temperature, middle section, leukocyte count in thousands, and lower section, titer for sheep cell agglutinins

Comment —Case 26 represents a moderately severe attack of infectious mononucleosis in which fever, prostration and splenic enlargement were marked, the blood picture characteristic and the sheep cell agglutinin titer high. It is notable that on the third day of definite illness, although the blood picture definitely suggested mononucleosis, the clinical picture was not suggestive and the test for sheep cell agglutinins was negative.

For comparison with this patient another may be cited

This patient, a man aged 22 years, a student, at no time felt ill except for sore throat, and the maximum temperature was 99.5 F. Nevertheless the blood picture was characteristic and extreme, and the sheep cell agglutinins reached a maximum titer of 1:5,120.

SUMMARY

1 A brief presentation of the clinical and cytologic aspects of infectious mononucleosis, based on a study of 28 sporadic cases of the disease, and a more extended report of serologic investigations of the disease are submitted

2 The morphologic characteristics of the predominant blood cell at the height of the disease suggest that it is an immature lymphocyte

3 Supravital staining methods employed in one case support this view

4 Evidence of amitosis of lymphocytes in the circulating blood stream similar to that noted in lymphatic leukemia is presented

5 It is demonstrated that the agglutination of sheep cells by normal human serum is greatly influenced by the concentration of cells used and the temperature at which the serum is incubated

6 The agglutination of sheep cells by normal human serum at low temperatures is reversible at 37.5 C in most cases

7 Serum from patients with infectious mononucleosis agglutinates sheep cells equally well at 5 C and at 37.5 C

8 Certain changes in the technic of the serologic test for infectious mononucleosis are proposed

9 It is pointed out that the serologic test without confirmatory clinical and cytologic findings may result in false diagnoses

10 Certain facts must be explained before the heterophile nature of the antibody in mononucleosis can be unreservedly accepted

Alex M. Burgess Jr prepared the plates and applied the supravital staining technic in case 26. Miss Evelyn Goodale assisted in the serologic work and E. G. E. Anderson of the Charles V. Chapin Hospital furnished materials during the course of the work.

CONCENTRATION OF SERUM PROTEIN IN DIFFERENT TYPES OF EDEMA

ILLUSTRATIVE CASES

HAROLD M. HAND, M.D.

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In 1895 Starling¹ first advanced his theory of the production of edema and the exchange of fluids between the blood and the tissue spaces. He showed that the colloid osmotic pressure of the serum was proportional to the concentration of protein in the serum. He advanced the theory that a decrease in the colloid osmotic pressure was responsible for the loss of fluid into the tissues and the production of edema. He contended that the crystalloids, though having a high osmotic pressure, have little influence on the exchange of water, because they pass through the walls of the vessels with the water, while the proteins, although having a much lower osmotic pressure, exert the principal influence because they do not pass through the walls of the vessels. Starling was unable to reduce the edema in the edematous leg of a dog by perfusion with Ringer's solution, but when perfusion with serum was done, the edema was reabsorbed.

Shade and Clausen² and Govaerts³ measured the colloid osmotic pressure and found it roughly proportional to the concentration of protein in the serum. They also found that the colloid osmotic pressure, or what they called the oncotic pressure, could be closely correlated with the development of edema. Govaerts also determined the amount of colloid osmotic pressure exerted by albumin and by globulin. He estimated that 1 Gm. of albumin per hundred cubic centimeters exerted a colloid osmotic pressure of 7.54 cm. of water, and 1 Gm. of globulin

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1 Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19**:312, 1895-1896.

2 Shade, H., and Clausen, F. Der onkotische Druck des Blutplasmas und die Entstehung der renalbedingten Odeme, *Ztschr. f. klin. Med.* **100**:363, 1924.

3 Govaerts, P. Influence de la teneur du sérum en albumines et en globulines sur la pression osmotique des protéines et sur la formation des oedemes, *Bull. Acad. roy. de méd. de Belgique* **7**:356, 1927.

per hundred cubic centimeters, a pressure of 195 cm of water. In other words, albumin exerts roughly four times as much osmotic pressure as globulin. This is consistent with its lesser molecular weight, and is of importance because it helps to explain the tendency of edema to parallel more closely the albumin than the globulin level.

The explanation of the interchange of fluids between the blood stream and the tissue and lymph spaces, according to the theory of Starling, Govaeits and Shade and Clausen, is dependent on the interbalance between two principal factors: the hydrostatic pressure (blood pressure) at the arterial end of the capillary, which tends to drive fluids through the capillary wall into the tissues, and the osmotic (or oncotic) pressure exerted by the nondiffusible proteins, which tends to draw water from the tissues into the blood stream. 1 Normally the hydrostatic pressure at the arterial end of the capillary drives fluid into the tissues, but as this pressure becomes dissipated the colloid osmotic pressure exerted by the proteins (if in normal concentration) is able to resist the hydrostatic pressure and, toward the venous side of the capillary, to draw fluids back into the blood stream. 2 If the concentration of serum protein is low the effective colloid osmotic pressure is reduced and consequently is unable to counterbalance the hydrostatic pressure. 3 If the venous pressure is increased, as in cardiac failure or venous obstruction, the hydrostatic pressure will be much higher than normal toward the venous side of the capillary, the normal osmotic pressure will be unable to return fluid into the capillary, and edema will result. 4 In case of injury or inflammation of the capillary wall it is thought that increased permeability results and that proteins to which the capillary wall is normally impermeable pass into the tissue spaces. This decreases the osmotic pressure in the capillary owing to the loss of proteins, and also decreases the effective osmotic pressure because the amount of protein in the tissue spaces is exerting an opposing osmotic pressure which must be overcome in addition to the hydrostatic pressure.

According to this concept anything which decreases hydrostatic pressure or increases osmotic pressure in the capillaries will cause absorption of fluid, while anything which increases hydrostatic pressure or lowers osmotic pressure, as well as anything which increases capillary permeability, will favor loss of fluid into the tissue spaces and edema.

Landis⁴ measured the rate and direction of the exchange of fluid between the capillaries of the mesentery of a frog and the tissue spaces and also the capillary pressure. He found that following three

⁴ Landis, E. M. Micro Injection Studies of Capillary Permeability. III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to the Plasma Proteins, *Am J Physiol* **83** 528, 1928.

minutes of lack of oxygen the permeability of the capillary wall was greatly increased. This allowed fluid to filter through at approximately four times the normal rate and also permitted the passage of proteins through the wall, thus reducing the effective osmotic pressure of the plasma proteins to about half the normal value. However, this movement of fluid through the asphyxiated capillary wall was proportional to the difference between the capillary pressure and the effective osmotic pressure.

The theory of Starling was given its first practical application by Epstein⁵ in explaining the production of edema in nephrosis, in which he found the levels of the serum proteins low. Kohman⁶ produced edema in rats by diets very low in proteins and, in some, by a synthetic diet complete in every respect except for proteins. This work was confirmed by Frisch, Mendel and Peters,⁷ who also demonstrated that the serum protein values were lowered about 40 per cent from those at the start of the experiment.

Leiter,⁸ Darrow, Hooper and Cary⁹ and Lepore¹⁰ produced edema by repeated plasmapheresis in dogs, that is, by bleeding the dogs, centrifugating the blood, suspending the erythrocytes in saline or in Locke's solution and reinjecting this into the dogs intravenously. Edema occurred when the serum protein levels were lowered by this method to from 3 to 4 Gm per hundred cubic centimeters. Darrow, Hooper and Cary⁹ concluded that dogs rendered edematous by plasmapheresis show a type of edema closely analogous to that of nephrosis, hydropigenous nephritis, nutritional edema and cachectic states, and that the low plasma protein level is not a cause of permanent renal damage. Leiter,^{8b} in his later experiments, showed that the edema fluid contained almost no protein. This observation indicates that the capillary wall has not become permeable to protein in this type of edema.

5 Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, Method for Its Alleviation, *Am J M Sc* **154** 638, 1917, Further Observations on the Nature and Treatment of Chronic Nephrosis, *ibid* **163** 167, 1922.

6 Kohman, E. A. The Experimental Production of Edema as Related to Protein Deficiency, *Am J Physiol* **51** 378, 1920.

7 Frisch, R. A., Mendel, L. B., and Peters, J. P. The Production of Edema and Serum Protein Deficiency in White Rats by Low Protein Diets, *J Biol Chem* **84** 167, 1929.

8 Leiter, L. (a) Experimental Edema, *Proc Soc Exper Biol & Med* **26** 173, 1928, (b) Experimental Nephrotic Edema, *Arch Int Med* **48**:1 (July) 1931.

9 Darrow, D. C., Hooper, E. B., and Cary, M. K. Plasmapheresis Edema I. The Relation of Reduction of Serum Proteins to Edema and the Pathological Anatomy Accompanying Plasmapheresis, *J Clin Investigation* **11** 683, 1932.

10 Lepore, M. J. Experimental Edema Produced by Plasma Protein Depletion, *Arch Int Med* **50** 488 (Sept) 1932.

ORIGIN AND REGENERATION OF PLASMA PROTEIN

The origin of the plasma proteins is not definitely known. Some believe that they are formed in the liver, as has been shown definitely to be the case with fibrinogen by Whipple and his co-workers. Others believe that they are produced by the blood-forming organs or by the intestinal mucosa. It is known that normal endothelium, with the exception of that of the capillaries of the liver, the intestinal mucosa and possibly the lungs, is impermeable to the plasma proteins and that the capillaries of the bone marrow, spleen and blood-forming organs are as a whole permeable to the formed elements of the blood, and may be assumed to be permeable to the plasma protein.¹¹ Although there is no direct evidence concerning the origin of these proteins the many conditions effecting their depletion and regeneration suggest that the production of albumin and that of globulin, if not independent processes, are at least controlled by different influences.¹²

NORMAL RANGE OF PLASMA PROTEIN VALUES

Moore and Van Slyke,¹³ investigating the normal range of plasma protein values, gave the results of their determinations on 9 normal subjects. They also gave those of Linder, Lundsgaard and Van Slyke on 8 normal persons and of Salvesen on 32 normal men and women. In averaging these they found that the three sets of data appear to fix with satisfactory agreement the normal plasma protein values in grams per hundred cubic centimeters at total protein, from 6.2 to 8, albumin, from 3.6 to 5, globulin, from 2 to 3.5, albumin-globulin quotient, from 1.2 to 2.2.

LOW SERUM PROTEIN VALUES IN VARIOUS CLINICAL CONDITIONS

In many clinical conditions one finds a lowered level of serum protein. Associated with this lowered level, if it is sufficiently marked, one finds edema. If one attempts to explain these obscure edemas on the Starling theory and hypoproteinemia one should consider such edemas in the light of the probable cause of the deficiency of serum protein. Low levels of serum protein may result from (1) insufficient protein intake owing to an inadequate diet, (2) excessive loss of protein through proteinuria, diarrhea or hemorrhage, (3) excessive

11 Krogh, A. *The Anatomy and Physiology of Capillaries*, New Haven, Conn., Yale University Press, 1924, p. 230.

12 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 1, pp. 655 and 688.

13 Moore, N. S., and Van Slyke, D. D. *The Relationships Between Plasma Protein Content, Plasma Specific Gravity, and Edema in Nephritis*, *J. Clin. Investigation* 8: 337, 1930.

metabolic wastage or destruction of protein in chronic infections or cachectic states; (4) inadequate assimilation of protein or decreased formation of protein

Insufficient Protein Intake—Edema has long been observed to occur during war and famine. It was common in central Europe during the World War. Park¹⁴ observed over 400 cases in a German prison camp. The rations were low in protein and almost fat-free. The rations

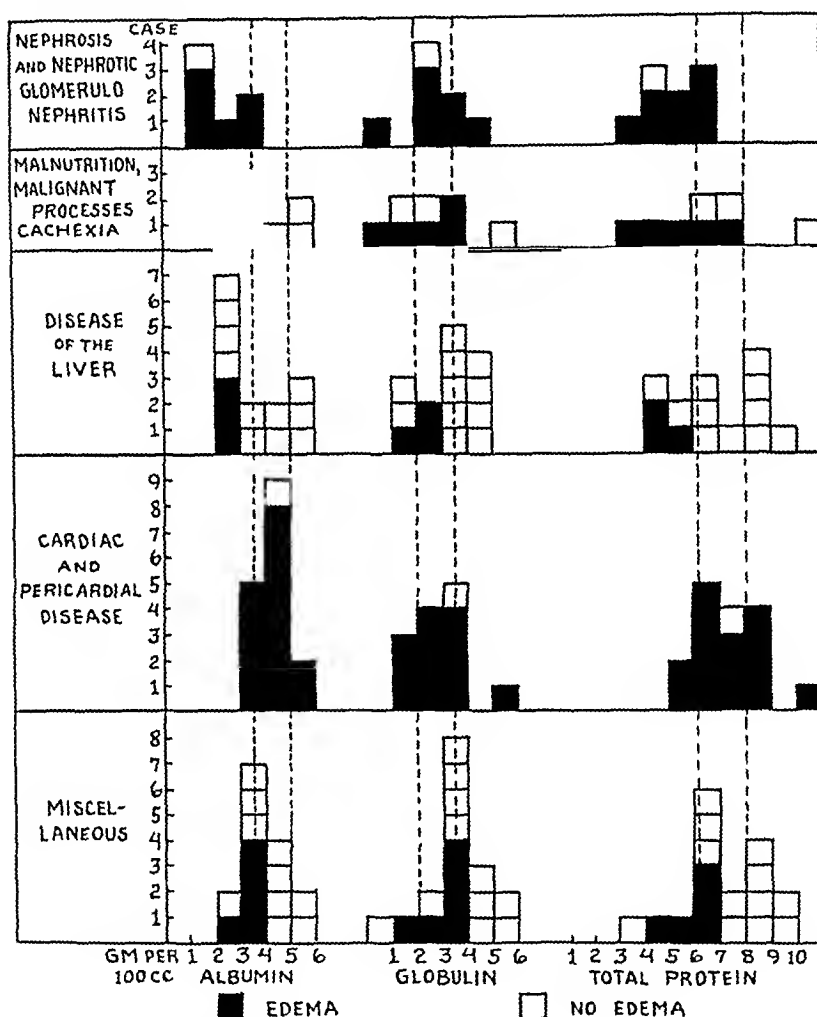


Chart 1—Serum protein levels in different clinical conditions with which edema is often associated. The cases in which edema occurred are represented by black squares, those in which no edema occurred, by white squares. The protein level in each group of cases is read from left to right. The level indicated between the broken lines is the normal level. Note that practically all the cases in which edema occurred except those of the cardiac group showed deficits of serum albumin and total protein.

were taken mostly in the form of soup, thus requiring ingestion of a large amount of fluid to obtain a small amount of nourishment. Park

¹⁴ Park, F. S. War Edema (Kriegsoedem), J. A. M. A. **70** 1826 (June 15) 1918.

considered the edema to be due to the deficient diet and to ingestion of a large amount of fluid and salt, but did not relate it specifically to the protein intake or to the serum protein level. By refractometric reading of war edema Schittenhelm and Schlecht¹⁵ estimated that the protein levels were reduced to from 4 to 6 Gm per hundred cubic centimeters. They also found that increased protein and fat in the diet was the principal factor in relieving the edema. Jansen¹⁶ made similar observations on the serum protein level in war edema, and also found that the patients were often in a condition of negative nitrogen balance. In fact, it has been estimated by Lusk¹⁷ that the average diet in Germany during the latter part of the war contained only 31.1 Gm of protein per day.

Weech and Ling,¹⁸ who studied a series of cases of nutritional edema during both the active and the convalescent stages, in China, found that the critical protein level of edema was close to 5 Gm per hundred cubic centimeters. They also found that the edema followed the albumin level more closely than the total protein or the globulin level. When the albumin level was greater than 2.9 Gm edema was never observed, but when the level fell below 2.5 Gm edema was invariably present. The edema was made worse by the administration of sodium chloride or sodium bicarbonate when the serum proteins were low, but these effects could not be produced after the administration of an adequate diet had resulted in a return of the serum proteins to normal levels. Liu, Chu, Wang and Chung,¹⁹ in a study of nutritional edema in China, found the edema and the serum protein level related to the protein intake. They also found that 1 Gm of animal protein is equivalent to 2 Gm of vegetable protein in increasing the plasma proteins. More recently, Youmans²⁰ and Youmans, Bell, Donley and Frank²¹ made a study of what they believed to be endemic nutritional edema in Tennessee. The diets of their patients were found to be low both in protein and in total

15 Schittenhelm, A., and Schlecht, H. Ueber Oedemkrankheit mit hypotonischer Bradykardie, *Berl klin Wchnschr* **55** 1138, 1918.

16 Jansen, W. H. Die Oedemkrankheit, *Deutsches Arch f klin Med* **131** 144, 1919.

17 Lusk, G. *Physiol Rev* **1** 523, 1921.

18 Weech, A. A., and Ling, S. M. Nutritional Edema. Observations on the Relation of the Serum Proteins to the Occurrence and to the Effect of Certain Inorganic Salts, *J Clin Investigation* **10** 869, 1931.

19 Liu, S. H., Chu, H. I., Wang, S. H., and Chung, H. L. Nutritional Edema. I Effect of Level and Quality of Protein Intake on Nitrogen Balance, Plasma Proteins and Edema, *Proc Soc Exper Biol & Med* **29** 250, 1931.

20 Youmans, J. B. Endemic Edema, *J A M A* **99** 883 (Sept 10) 1932.

21 Youmans, J. B., Bell, A., Donley, D., and Frank, H. Endemic Nutritional Edema. I Clinical Findings and Dietary Studies, *Arch Int Med* **50** 843 (Dec) 1932. II Serum Proteins and Nitrogen Balance, *ibid* **51** 45, 1933.

calories The total serum protein was usually within the normal range, but the albumin and the computed colloid osmotic pressure were below normal An increased intake of protein caused a rise in serum albumin and a disappearance of the edema

Cardiac edema is ordinarily accompanied by an increase in venous pressure Theoretically this increase raises the hydrostatic pressure at the venous end of the capillary bed and edema cannot be prevented even though the serum protein values and the colloid osmotic pressure are normal If the serum protein values are also reduced, as they occasionally are, one expects to find the cardiac edema increased by this additional nutritional factor Krogh, Landis and Turner²² showed that fluid accumulates in the tissue spaces when the average venous pressure is above 17 cm of water, and Landis, Jonas, Angevine and Erb²³ showed that the permeability of the capillary wall with respect to protein varies with the grade of venous congestion, and that the loss of fluid from the blood is conspicuously greater at higher venous pressures

Lack of oxygen, by causing increased permeability of the capillaries, may also be a considerable factor in the production of cardiac edema Landis⁴ showed that lack of oxygen increases the permeability of the capillaries and also causes the capillaries to become permeable to protein, thus reducing the effective osmotic pressure of the plasma proteins Payne and Peters²⁴ called attention to the fact that the serous effusions from patients with cardiac failure contain distinctly higher concentrations of protein than do the almost protein-free effusions of nephrosis, and hence the "effective oncotic pressure" of the serum is decreased It is evident, as they suggested that cardiac edema may occur at any protein level if the back pressure or increased venous pressure causes sufficient rise in the capillary pressure However, this can proceed only to the point at which the mean capillary pressure equals the oncotic pressure If the oncotic pressure is reduced by reason of a deficiency of serum protein, the same degree of congestion will produce a greater degree of edema In 62 determinations on patients with varying degrees of cardiac failure Ellis²⁵ found that although edema

22 Krogh, A , Landis, E M , and Turner, A H The Movement of Fluid Through the Human Capillary Wall in Relation to the Venous Pressure and to the Colloid Osmotic Pressure of the Blood, *J Clin Investigation* **11**:63, 1932

23 Landis, E M , Jonas, L , Angevine, M , and Erb, W The Passage of Fluid and Protein Through the Human Capillary Wall During Venous Congestion, *J Clin Investigation* **11** 717, 1932

24 Payne, S A , and Peters, J P Plasma Proteins in Relation to Blood Hydration VIII Serum Proteins in Heart Disease, *J Clin Investigation* **11**. 103, 1932

25 Ellis, L B Plasma Protein Deficiency in Patients with Cardiac Edema, *M Clin North America* **16** 943, 1933

frequently existed when the plasma proteins were above 5 Gm per hundred cubic centimeters owing to the mechanically increased venous pressure, edema was always present when the proteins were below 5 Gm. Ellis also noted that the severe and stubborn cases of cardiac edema are frequently associated with low serum proteins.

The low levels of the serum proteins in some cases of cardiac edema probably result from the low intake of protein, sometimes for a period of years, especially in cases of hypertensive cardiovascular disease. With the beginning of congestive failure and resulting anorexia the protein intake is often further restricted, and the case becomes one of malnutrition, with nutritional as well as cardiac edema. It would seem logical in cases of cardiac failure with edema to give a diet adequate in protein as well as high in carbohydrate. With care this can usually be accomplished in spite of the tendency to anorexia, and also without giving an excess of salt and fluid. In cases with marked lowering of the serum protein levels adequate protein in the diet is of great assistance, in addition to the regular treatment of congestive failure, in eliminating the edema which otherwise is rather stubborn. In view of these facts, and considering the work of Keutmann and McCann,²⁶ the common practice of marked restriction of protein intake in cases of hypertensive cardiovascular disease without retention of nitrogen would seem to be unjustifiable and at times harmful.

The cases of cardiac disease with edema in the present study are listed in table 4. There are only 2 or 3 in which there was a sufficient deficit of serum protein for it to be considered a possible additional factor in the production of the edema. Case 23 is of interest. The patient had constrictive pericarditis with calcification of the pericardium, ascites and edema of the scrotum and extremities. He also had a considerable deficit of serum protein. He was improved following cardiolytic, but the edema did not entirely disappear until the serum protein levels had returned to normal on a diet high in protein.

Diabetic edema is now seen much less often than before the use of insulin. This is probably because, with insulin, one is able to give patients a normal caloric intake, while formerly patients with moderately severe diabetes had to be maintained in a state of chronic malnutrition. Peters, Bulger and Eisenman²⁷ found the serum protein values normal in mild cases of diabetes unassociated with ketosis or malnutrition, but decreased in severe cases associated with chronic malnutrition. Bruck-

26 Keutmann, E. H., and McCann, W. S. Dietary Protein in Hemorrhagic Bright's Disease, *J. Clin. Investigation* **11** 973, 1932.

27 Peters, J. P., Bulger, H. A., and Eisenman, A. J. The Plasma Proteins in Relation to Blood Hydration. II. In Diabetes Mellitus, *J. Clin. Investigation* **1** 451, 1925.

man, D'Esopo and Peters²⁸ also found the serum protein values low in cases of diabetes with malnutrition, the deficit being principally in the albumin fraction. These workers also noted that with diabetic acidosis edema was seldom if ever seen, and that with acidosis and accompanying dehydration there was hemoconcentration and a serum protein level above that found when normal hydration was restored. Consequently the edema was usually seen in the absence of acidosis and dehydration or after the acidosis and dehydration had been relieved. However, in all cases of diabetes with edema there was low serum protein. Joslin and Goodall,²⁹ in 1908, found when treating diabetic

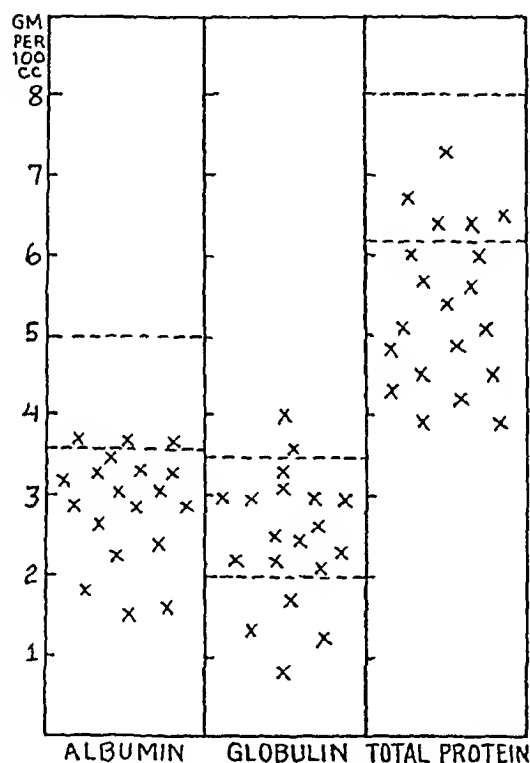


Chart 2—Serum protein levels in noncardiac cases of edema. The crosses represent cases. The space between the broken lines represents the normal range of the protein level.

acidosis with sodium bicarbonate that edema developed in some of the patients while in others it did not. Hence they concluded that some factor other than the sodium bicarbonate must have been responsible for the edema. Although they did not, at that time, make serum

28 Bruckman, F. S., D'Esopo, L. M., and Peters, J. P. The Plasma Proteins in Relation to Blood Hydration. IV. Malnutrition and the Serum Proteins, *J. Clin. Investigation* 8: 577, 1930.

29 Joslin, E. P., and Goodall, H. W. Experiments on an Ash-Free Diet and Salt Metabolism with Especial Reference to Edema in Diabetes Mellitus, *J. A. M. A.* 51: 727 (Aug. 29) 1908.

protein determinations, it seems probable that the patients with edema might have had low serum protein levels

Vomiting and anorexia, if they have persisted long enough, may result in malnutrition and hypoproteinemia due to inadequate intake of protein. This is well illustrated in case 6, table 2. This patient with linitis plastica due to scirrhus carcinoma or syphilis of the stomach gave a history of vomiting nearly everything he had eaten for from two to three months before admission. He had edema, bradycardia and somnolence, and the total serum protein amounted to 3.93 Gm of which 2.96 Gm was albumin. Although the malnutrition and hypoproteinemia might have been due to the gastric lesion, it seems more probable that the decrease in the protein intake due to the vomiting was the principal factor, since on a diet high in protein the edema disappeared, the serum protein levels returned to normal and the patient felt so well that he left the hospital against advice.

Excessive Loss of Protein—Although others had previously noted hypoproteinemia and excessive albuminuria in certain cases of nephritis with edema, Epstein was the first to explain the edema in these cases as caused by hypoproteinemia, according to the Starling theory. One of the chief objections to the explanation of nephrotic edema on the basis of hypoproteinemia is the well known fact that early in acute nephritis edema is present with a normal level of serum proteins. However, it has been shown that the edema fluid in acute nephritis contains protein in a relatively high concentration, instead of being a practically protein-free filtrate of the blood plasma as is the edema fluid of nephrosis and malnutrition^{30a}. This indicates that an increased capillary permeability is responsible for the edema of nephritis, which is in keeping with the presence of hemorrhages and exudate in the retina, hematuria, hypertension and other evidences of involvement of the general vascular system rather than with a lesion confined only to the kidney. It has been shown that the edema of acute nephritis, if persistent, will become associated with low serum protein levels caused by proteinuria and malnutrition³¹.

Peters³² and his associates showed that the reduction of the serum proteins at the expense of the albumin fraction is not characteristic of idiopathic nephrosis, but is equally or more common in other types

30 Peters, J. P. (a) Salt and Water Metabolism in Nephritis, *Medicine* **11** 435, 1932, (b) *ibid*, footnotes 280 and 281.

31 Peters, J. P., Bruckman, F. S., Eisenman, A. J., Hald, P. M., and Wakeman, A. M. The Plasma Proteins in Relation to Blood Hydration. VII. A Note on the Proteins in Acute Nephritis, *J. Clin. Investigation* **11** 97, 1932.

32 Peters, J. P., Bruckman, F. S., Eisenman, A. J., Hald, P. M., and Wakeman, A. M. The Plasma Proteins in Relation to Blood Hydration. VI. Serum Proteins in Nephritic Edema, *J. Clin. Investigation* **10** 941, 1931.

of nephritis with noncardiac edema, such as the nephrotic type of chronic glomerulonephritis or amyloid disease of the kidneys. It is probable that the reason the edema is associated with a deficit of albumin rather than with a decrease of globulin is that the protein in the urine is mostly albumin. According to Hiller, McIntosh and Van Slyke,³³ from 85 to 90 per cent of the protein in the urine is albumin, while only from 10 to 15 per cent is globulin. However, the degree of the deficit of albumin is not entirely related to the amount of proteinuria in all cases,³² although this is undoubtedly the most important factor in the deficit, many patients show unmistakable malnutrition. Peters³² and his associates found that when the serum protein level, by reason of a deficit of albumin, fell below 5 Gm per hundred cubic centimeters, edema was usually present. When the protein level was between 4 and 5 Gm, the edema could usually be eliminated by therapeutic measures, but when it fell below 4 Gm, treatment was usually ineffectual. In a study of 75 cases of various types of nephritis, hemorrhagic, degenerative and arteriosclerotic, Moore and Van Slyke¹³ found that when the total protein content fell below 5.5 ± 0.3 Gm, or the albumin below 2.5 ± 0.2 Gm, or the specific gravity below 1.023 ± 0.0003 , edema was usually present. A few exceptions to this rule were found. 1. During the first few weeks of acute hemorrhagic nephritis, or during exacerbations of chronic hemorrhagic nephritis due to injury or infection, a transient edema may be seen before the critical levels have been reached. 2. When the serum globulin is involved so that changes in the total protein do not parallel the changes in the albumin level, the tendency to edema parallels only the albumin level. 3. Restriction of salt may cause the edema to be absent, with the serum proteins below the critical level, however, this usually causes only partial disappearance of the edema.

The cases of nephrosis in the present study are listed in table 1. In the cases with edema the proteins were at or below the critical level except in case 5, in which they were slightly above this level.

Peters, Wakeman, Eisenman and Lee³⁴ mentioned the disappearance of edema during terminal infections without any appreciable change in the concentration of the serum protein. (This point is well illustrated in case 2, table 1. With the nephrotic type of glomerulonephritis already present primary peritonitis developed in this patient, and the edema rapidly disappeared, although the serum proteins were well below the

33 Hiller, A., McIntosh, J. F., and Van Slyke, D. D. The Excretion of Albumin and Globulin in Nephritis, *J. Clin. Investigation* 4: 235, 1927.

34 Peters, J. P., Wakeman, A. M., Eisenman, A. J., and Lee, C. Total Acid-Base Equilibrium of Plasma in Health and Disease. XII. A Study of Renal Edema, *J. Clin. Investigation* 6: 577, 1929.

critical level and even a little lower than before the onset of the terminal infection) The same investigators also showed that with extreme hypoproteinemia the tendency to transudation becomes so marked that neither the onset of vomiting nor the use of acid diuretics, although they may cause marked hemoconcentration, produces much, if any, diuresis In the terminal stages of nephritis the reduction of serum protein at the expense of the albumin fraction is common³⁵ and, in some cases, is marked as in nephrosis However, it is not possible to correlate this with the presence of edema because of the many variable and complicating factors, such as heart failure, malnutrition, marked hemoconcentration and rapidly changing electrolytic patterns

Excessive protein may be lost by way of the gastro-intestinal tract because of diarrhea or hemorrhage Low serum protein levels are not

TABLE 1—Group 1 Nephrotic Glomerulonephritis

Case	Diagnosis and Progress	Edema	Total Serum Protein, Gm	Albu min, Gm	Glob ulin, Gm	Albumin Globulin Ratio
1	Subacute glomerulonephritis	+1	5.70	3.26	2.44	1.134
2	Nephrotic type of chronic glomerulonephritis	+2	5.59	1.75	4.01	1.039
	On readmission, 3 months later	+2	4.38	1.87	2.66	1.05
	On readmission 1 month later, with primary pneumococcal peritonitis, carbon dioxide combining power, 39 per cent by volume, no edema	0	4.40	1.90	2.5	1.076
3	Subacute glomerulonephritis	+1	4.21	3.33	0.88	1.37
4	Nephrotic type of chronic glomerulonephritis	+2	3.90	1.58	2.32	1.07
5	Nephrotic type of chronic glomerulonephritis	+2	6.09	2.94	3.15	1.093
	After being on a diet high in protein	+1	6.40	3.13	3.27	1.093
	After being on a diet high in protein	0	6.85			

frequently noted, however, probably because of the hemoconcentration caused by the severe dehydration, which masks the true serum protein levels The dehydration and hemoconcentration are probably further increased by the acidosis caused by the loss of total base In cases of diabetes with malnutrition the presence of acidosis and dehydration is known to mask the serum protein levels and edema, and low serum protein levels may be found after the restoration of normal hydration²⁸ A similar mechanism is suggested by the occasional appearance of edema in infants with severe diarrhea after the dehydration has been overcome Chester Jones³⁶ mentioned low serum protein levels with edema as one of the many complications of chronic ulcerative colitis Moschcowitz³⁷ cited 3 cases of chronic ulcerative colitis with low

³⁵ Peters, J. P., Bruckman, F. S., Eisenman, A. J., Hald, P. M., and Wakeman, A. M. The Plasma Proteins in Relation to Blood Hydration. IX. Serum Proteins in the Terminal Stages of Renal Disease, *J. Clin. Investigation* **11**: 113, 1932

³⁶ Jones, C. M. Peripheral Complications of Ulcerative Colitis, *M. Clin. North America* **16**: 919, 1933

³⁷ Moschcowitz, E. Hypoproteinemia, *J. A. M. A.* **100**: 1086 (April 8) 1933

serum protein levels and edema. Edema and hypoproteinemia developed in 2 of the cases which I examined (34 and 35, table 5) following ileostomy for severe idiopathic ulcerative colitis. Owing to the excessive loss of protein in this disease it would seem important to see that these patients receive an adequate amount of protein to combat the tendency to hypoproteinemia. Moschcowitz suggested that chronic hemorrhage from the gastro-intestinal tract, as with ulcer and carcinoma, may produce low serum protein levels and edema. However, since the tendency to hypoproteinemia and edema does not parallel the degree of anemia it is probable that factors other than the direct loss of protein by hemorrhage, such as malnutrition due to inadequate intake or metabolic waste of protein play an important part.

TABLE 2—Group 2 Malnutrition, Malignant Tumor and Cachexia

Case	Diagnosis and Progress	Edema	Total Serum Protein, Gm	Albumin, Gm	Globulin, Gm	Albumin Globulin Ratio
6	Linitis plastica due to scirrhus carcinoma or syphilis of the stomach	+2	3.93	2.96	0.97	1.3
	After being on a diet high in protein	0	7.3	5.28	2.06	1.25
7	Hodgkin's disease, ascites, edema of lower extremities, postmortem, the glands were seen surrounding and pressing on the iliac vessels	+1	7.34	3.71	3.63	1.102
8	Carcinoma of the colon, metastasis to the liver, emaciation and dehydration	0	10.56	5.07	5.49	1.092
9	Tertiary syphilis, diet low in protein and in calories	+1	6.72	3.72	3.00	1.123
10	Carcinomatosis	+2	5.16	2.92	2.24	1.13
11	Carcinoma of the stomach, with metastasis	0	6.78	4.92	1.86	1.264
12	Carcinoma of the sigmoid, cachexia	+2	4.53	3.33	1.20	1.27

Excessive Destruction and Metabolic Wastage of Proteins—In cases of chronic infection with malnutrition the serum protein levels are usually decreased and edema is occasionally seen. This was found by Bruckman, D'Esopo and Peters²⁸ in cases of tuberculosis with malnutrition. They also found a marked tendency to increased globulin in conditions caused by chronic infection. Landis and Leopold³⁸ found the serum protein level as low as 3.6 Gm per hundred cubic centimeters in a case of tuberculous enteritis with a restricted diet. Wolferth³⁹ reported low serum protein levels and edema in patients with fecal fistulas and emaciation. In 124 determinations on 57 patients who showed evidence of malnutrition Bruckman, D'Esopo and Peters found the total serum protein level reduced, and in this reduction the albumin fraction alone suffered except in the cases associated with infection,

38 Landis, E. M., and Leopold, S. S. Inanition Edema Associated with Tuberculous Enteritis, *J. A. M. A.* 94:1378 (May 3) 1930.

39 Wolferth, C. C. Inanition Edema Associated with Alimentary Disturbances in Adults, *M. Clin. North America* 8:785, 1924.

as mentioned previously, in which the globulin tended to be increased. They found that in the cases of malnutrition the administration of a high caloric diet with a large proportion of protein caused a gradual rise in the serum albumin as nutrition improved. Bruckman and Peters⁴⁰ concluded that malnutritional or cachectic edema is referable to a deficiency of serum albumin brought about by a wastage of body protein, the result of disease or of inadequate diet. That wastage of body protein is probably an important factor is suggested by the gradual fall of serum protein levels in cases of carcinoma in which cachexia develops in spite of a caloric and protein intake which would be adequate for a normal person. This is well illustrated in case 16, table 3, and case 10, table 2. With carcinoma of the head of the pancreas and carcinomatosis, respectively, the serum protein levels dropped in spite of every effort to keep up an adequate protein and caloric intake.

The cases of malnutrition, malignant processes and cachexia are listed in table 2. Those with edema showed a pronounced deficit of serum protein except case 7 in which the edema was due to the pressure of tumor tissue on the iliac vessels.

Inadequate Assimilation of Protein or Decreased Formation of Protein—Since the site of the formation of the plasma proteins is not known except in the case of fibrinogen, which Foster and Whipple⁴¹ showed definitely to be formed by the liver, one can only speculate as to the possibility of deficits of serum protein being at times due to inadequate formation. Likewise, inadequate assimilation of protein owing to some gastro-intestinal defect can be no more than suspected.

However, it is interesting to note the sudden drop in serum proteins and more especially in the albumin in cases of severe damage to the liver, such as acute yellow atrophy. This is well illustrated in case 19, table 3, in which the patient had ingested from 4 to 6 ounces (125 to 185 cc) of chloroform. A day or two after the development of intense jaundice the serum proteins totaled 5.66 Gm per hundred cubic centimeters, of which 4.56 Gm was albumin. Two days later the proteins had dropped to 4.31 Gm, of which 2.82 Gm was albumin. In case 13, table 3, in which the patient died of acute yellow atrophy caused by cinchophen, the serum proteins dropped to 5.15 Gm, of which 2.94 Gm was albumin. In these cases it seems possible that the toxic agent depressed the source of the formation of serum proteins,

40 Bruckman, F. S., and Peters, J. P. The Plasma Proteins in Relation to Blood Hydration. V. Serum Proteins and Malnutritional or Cachectic Edema, *J. Clin. Investigation* 8: 591, 1930.

41 Foster, D. P., and Whipple, G. H. Blood Fibrin Studies. IV. Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury and the Eck Fistula. Notes Concerning the Origin of Fibrinogen in the Body, *Am. J. Physiol.* 58: 407, 1922.

especially that of albumin, or possibly severe metabolic wastage accounted for the sudden drop in the serum proteins. The absence of marked loss of protein from the body and the rapid onset of a deficit of serum protein suggest that the liver may have much to do with the production of serum protein other than fibrinogen. Kumpf⁴² also recorded a case of acute yellow atrophy in which the serum proteins were very low, especially the albumin, causing a reversal of the albumin-globulin ratio. Moschcowitz³⁷ mentioned a patient who had Gaucher's disease and nodular cirrhosis with hypoproteinemia and edema. Peters, Bruckman, Eisenman, Hald and Wakeman³² mentioned a patient with cirrhosis of the liver who had generalized subcutaneous edema, in whose

TABLE 3—Group 3 Disease of the Liver

Case	Diagnosis and Progress	Edema	Total Serum Protein, Gm	Albumin, Gm	Globulin, Gm	Albumin Globulin Ratio
13	Acute yellow atrophy due to einchophen	+1	5.15	2.94	2.21	1.13
14	Syphilitic cirrhosis	0	8.59	5.07	3.52	1.14
15	Portal cirrhosis	0	8.28	3.71	4.57	1.081
		0	7.90	3.65	4.25	1.085
16	Carcinoma of the head of the pancreas with obstructive jaundice	0	9.22	5.26	3.96	1.13
	Three months later marked cachexia, malnutrition and edema	+2	4.37	2.68	1.68	1.15
17	Syphilitic cirrhosis of the liver, with ascites	0	6.56	2.57	3.98	1.064
18	Acute hepatitis, with marked jaundice	0	8.28	4.06	4.22	1.096
	Jaundice decreased, ascites present	0	6.56	2.84	3.72	1.076
	Ascites present, moderate edema of ankles	+2	4.84	2.32	2.57	1.092
	After increasing protein in the diet	0	6.65	2.37	4.28	1.055
19	Subacute yellow atrophy of the liver due to ingestion of chloroform with fatal outcome	0	5.66	4.56	1.10	1.41
	Acidosis, carbon dioxide combining power, 15 per cent by volume	0	4.31	2.84	1.42	1.19
20	Cirrhosis of the liver, with ascites	0	8.46	5.13	3.33	1.15

serum the total proteins varied between 5.9 and 7.23 Gm per hundred cubic centimeters while the albumin was very low, from 1.52 to 1.95 Gm, with the globulin making up the greater part of the proteins. Case 18 is interesting, the patient having been admitted to the hospital with acute hepatitis and marked jaundice, later developing into cirrhosis with ascites. During this time the serum proteins fell from 8.28 to 4.84 Gm per hundred cubic centimeters, and the albumin from 4.06 to 2.52 Gm, with the development of edema. The edema was probably not due entirely to the pressure of the ascitic fluid on the abdominal veins, since it was not present before the serum proteins became so low and did not improve appreciably when the ascitic fluid was removed by paracentesis. It is doubtful that the liver had any direct relation to the deficit of serum protein, since the patient was on a diet high in carbohydrate and low in protein and fat in an effort to combat the ascites.

⁴² Kumpf, A. E. The Blood Proteins with Special Reference to the Changes Occurring in Renal Diseases, Arch Path **11** 335 (March) 1931.

The idea that the deficit of serum protein was probably caused by a decrease in protein intake and perhaps by metabolic wastage is further strengthened by the marked improvement in the edema and the rise in the serum proteins when the protein in the diet was increased. Atchley, Loeb, Benedict and Palmer⁴³ noted a reduction of serum proteins in 3 cases of cirrhosis of the liver with ascites. Wiener and Wiener⁴⁴ found the albumin somewhat decreased and

TABLE 4—Group 4 Cardiac and Pericardiac Disease

Case	Diagnosis and Progress	Edema	Total Serum Protein, Gm	Albumin, Gm	Globulin, Gm	Albumin Globulin Ratio
21	Tuberculous pericarditis, with effusive and syphilitic cirrhosis	+1	10.8	4.62	6.18	1.075
	Tuberculous adhesive pericarditis and syphilitic cirrhosis, with generalized edema and ascites	+3 -3	8.1 7.06	5.45 3.91	3.35 4.05	1.16 1.096
22	Adhesive mediastinopericarditis, enlarged liver and spleen, edema of the face and lower extremities	-1	7.06	4.49	3.47	1.12
23	Constructive pericarditis, with calcified pericardium and edema of the serotum and lower extremities and ascites	+2	5.00	3.4	1.6	1.21
	After cardiolytic and increased intake of protein	0	7.95	4.25	3.67	1.12
24	Cardiac decompensation, palpable liver	+2	6.61	3.75	2.86	1.13
25	Arteriosclerotic cardiac disease, with decompensation and general anasarca	-4	6.18	3.27	2.91	1.11
26	Myocardial degeneration, inoperable carcinoma of the stomach, diabetes mellitus	+1	6.78	4.04	2.74	1.14
	After exploratory laparotomy	+2	6.25	4.04	2.21	1.18
27	Arteriosclerotic cardiac disease, with decompensation and general anasarca	+1	6.00	4.20	1.80	1.23
28	Cardiac decompensation	+3	7.70	3.90	3.80	1.10
29	Arteriosclerotic cardiac disease	+1	8.75	4.04	4.71	1.085
30	Arteriosclerotic cardiac disease	+1	8.9	4.78	4.12	1.11
31	Syphilitic aortitis	+1	6.38	1.86	1.52	1.3
32	Hypertension, myocardial degeneration	+1	8.82	5.76	3.06	1.19

the globulin increased in 12 cases of hepatic cirrhosis. However, there was no consistent marked deficit of serum protein. In cases of jaundice without an elevation of temperature they found the serum proteins normal in amount or increased, the albumin within normal limits and the globulin increased. It is apparent from the cases reported by various authors and from those which I have examined and listed in table 3 that the serum protein level in disease of the liver is quite variable. Except in cases of acute hepatic insufficiency such as acute or subacute atrophy of the liver in which the serum protein levels drop rapidly, there is no consistent deficit of serum protein in disease of the liver. When there is an appreciable deficit of protein in chronic

43 Atchley, D. W., Loeb, R. F., Benedict, E. M., and Palmer, W. W. Physical and Chemical Studies of Human Blood Serum. III. A Study of Miscellaneous Disease Conditions, *Arch. Int. Med.* **31**: 616 (April) 1923.

44 Wiener, H. J., and Wiener, R. E. Plasma Proteins, *Arch. Int. Med.* **46**: 236 (Aug.) 1930.

disease of the liver, it can usually be explained by accompanying malnutrition or by inadequacy of protein intake, since a diet low in protein is often employed as a therapeutic measure in these cases

Edema is frequently seen in cases of pernicious anemia. It is also seen at times in cases of idiopathic hypochromic anemia. In case 33, table 5, the patient had idiopathic hypochromic anemia with edema and serum proteins totaling 4.84 Gm per hundred cubic centimeters, of which 3.75 Gm was albumin and 1.3 Gm globulin. Peters, Eisenman and Bulger⁴⁵ found low plasma protein values 4 times in 7 observations on patients with profound anemia. They found no relation between the reduction of the proteins and the presence, severity or type of the

TABLE 5—Group 5 Miscellaneous Involvements

Case	Diagnosis and Progress	Edema	Total Serum Protein, Gm	Albumin, Gm	Globulin, Gm	Albumin Globulin Ratio
33	Idiopathic hypochromic anemia	+1	4.84	3.71	1.30	1.28
34	Ulcerative colitis, after ileostomy and administration of considerable salt solution	+2	5.40	2.24	2.16	1.103
35	Ulcerative colitis, following ileostomy	+2	6.40	3.38	3.02	1.11
36	Chronic ulcerative colitis	0	8.54	5.02	3.52	1.142
37	Chronic pemphigus	+1	6.00	3.00	3.00	1.1
38	Tuberculous peritonitis, plastic	0	6.71	3.91	2.80	1.13
39	Diabetes mellitus	0	6.90			
40	Plastic peritonitis (tuberculous?)	0	7.84	3.37	4.47	1.075
41	Lobar pneumonia	0	3.91	2.95	0.96	1.3
42	Acromegaly	0	8.20	3.9	4.3	1.09
43	Celiac disease, with a diet high in protein	0	9.68	4.49	5.19	1.086
	Celiac disease, with a diet high in protein	0	8.12	4.10	4.02	1.101
	Celiac disease, with exacerbation of symptoms, diarrhea, anorexia, loss of weight	+2	6.56	3.52	3.04	1.11
44	Tertiary syphilis, colonic stasis	0	9.56	5.30	4.26	1.12
45	Diabetes mellitus	0	6.90			
46	Diabetes mellitus, fibroma of the uterus	0	7.60	4.1	3.5	1.12
47	Pernicious anemia, red blood cells, 3,000,000	0	8.21	4.42	3.79	1.12

anemia. Meulengracht and his associates⁴⁶ found a low serum protein level in nearly all of 12 patients with pernicious anemia, and edema in 11. However, he found no constant relationship between the degree of anemia and that of edema. Moschcowitz,³⁷ after reviewing the work of several investigators, stated that the edema in pernicious anemia is sufficiently accounted for by a hypoproteinemia which is rather consistently present in this disease whether the malady is accompanied by edema or not. The cause of the hypoproteinemia is not known. It may be due to deficient formation, increased destruction or lack of adequate absorption

45 Peters, J. P., Eisenman, A. J., and Bulger, H. A. The Plasma Proteins in Relation to Blood Hydration. I. In Normal Individuals and in Miscellaneous Conditions, *J. Clin. Investigation* 1:435, 1925.

46 Meulengracht, E., Iversen, P., and Nakazawa, F. Pernicious Anemia. Edema and Reduction in Excretion of Water, *Arch. Int. Med.* 42:425 (Sept.) 1928.

or assimilation of protein from the gastro-intestinal tract Castle believed that in some cases of pernicious anemia and sprue there is, in addition to a lack of the intrinsic factor from the stomach or the extrinsic factor (dietary deficiency) or both, an improper intestinal absorption, and that in such cases recovery occurs only when liver extract is used parenterally. It is conceivable that improper intestinal absorption of protein might be an important factor in the production of the hypoproteinemia that so often accompanies pernicious anemia. Likewise, Strauss and Castle⁴⁷ believed that idiopathic hypochromic anemia may be due to direct dietary deficiency, or to indirect dietary deficiency conditioned by gastric anacidity and hypo-acidity, or to a factor associated with these defects. This might also explain the hypoproteinemia occasionally seen with hypochromic anemia. Marriott⁴⁸ believed that the edema frequently present in celiac disease is dependent on a low concentration of serum protein. This may be another example of hypoproteinemia and edema caused by inadequate absorption of protein from the gastro-intestinal tract. In case 43, table 5, in which the patient had celiac disease, there was no deficit of serum protein while the patient was under careful management, with a diet high in protein. However later there was an exacerbation of symptoms, with diarrhea, anorexia and loss of weight, and at that time a deficit of serum protein and edema developed.

THE RATIO OF ALBUMIN TO GLOBULIN

In experiments with plasmapheresis in dogs, Darlow, Hooper and Cary⁹ found the albumin and the globulin reduced in approximately the same proportions, but after the bleeding was stopped, the restoration of the globulin was more rapid than that of the albumin. Lepore¹⁰ found the same thing in slow plasmapheresis in dogs, but with moderately rapid plasmapheresis he found that the albumin was restored more quickly than the globulin during the first day or two, while later the globulin was restored more rapidly than the albumin. He suggested that the early emergency restoration is from the lymph. It has been shown by practically all those working on hypoproteinemia, both that due to the nephrotic syndrome and that due to malnutrition, that the deficit is in the albumin, and that the edema is more closely related to this deficit than to the level of the total proteins. The globulin is usually not decreased and is frequently slightly increased. This increase

47 Strauss, M. B., and Castle, W. B. Studies of Anemia in Pregnancy. III. The Etiologic Relationship of Gastric Secretory Defects and Dietary Deficiency to the Hypochromic and Macrocytic (Pernicious) Anemias of Pregnancy and the Treatment of These Conditions, *Am J M Sc* **185** 539, 1933.

48 Marriott, W. M. *Infant Nutrition*, St. Louis, C. V. Mosby & Company, 1930.

in the globulin is too frequent in hypoproteinemia to be regarded as always due to coincidental infection. It is probably in the nature of a compensatory response which, however, usually fails to prevent the occurrence of edema. Since the oncotic pressure of the albumin is about 4 times that of the globulin, one expects the tendency to edema to follow more closely the level of the albumin than that of the globulin or of the total proteins, but it is conceivable that a sufficient increase in the globulin might prevent the formation of edema in the face of a considerable deficit in the albumin. Salvesen⁴⁰ reported a case of nephrosis with syphilis which is often quoted to illustrate this point. The serum albumin level was only from 1.69 to 2.56 Gm per hundred cubic centimeters, but this was balanced by a globulin level of from 7.10 to 8.08 Gm, which kept the oncotic pressure up, and edema did not develop. As shown by Bruckman, D'Esopo and Peters,²⁸ in cases in which a marked increase in globulin is found, this is usually associated with infection. For that reason they found normal levels of the total proteins in certain patients with infectious diseases and malnutrition in spite of the presence of a definite deficiency in the serum albumin. As they suggested, it seems doubtful that the ratio of albumin to globulin is in itself of any great value. If the levels of albumin and globulin are influenced by different factors it would seem that the levels of the individual components and not their relative levels are important. Hence it is evident that a low albumin-globulin quotient due to an excess of globulin has an entirely different significance from one that is due to a deficiency of albumin.

OTHER FACTORS IN THE PRODUCTION OF NONCARDIAC EDEMA

The preponderance of evidence indicates that the principal and constant factor in producing a tendency toward noncardiac edema, either nephritic or nutritional, is a deficit of serum protein. However, there is another important factor, namely, the consumption of sodium chloride. In order to form edema fluid the organism must be supplied with the materials which make up this fluid, namely, salt and water. The organism is not inclined to retain water unless there is sufficient salt available to form an isotonic solution. This is evidenced by the fact that a large amount of water without salt may be drunk by an edematous nephrotic person without increase in the edema unless there has been a previous excess of salt in the diet. In fact, water given without salt not only may be excreted normally, but may sweep out of the body salt previously retained and with it extra water, causing a profuse diuresis.^{30a} This same thing was found by Schittenhelm and Schlecht¹⁵ in cases of

49 Salvesen, H. A. Hyperproteinemia in a Case of Nephrosis, *Acta med Scandinav* 65 152, 1926

famine edema. They also found that salt without water was well excreted, withdrawing water from the body, but that salt and water given together exaggerated the edema. It used to be thought that in nephritis the kidneys were unable to excrete chlorides and that as a result water was retained only after the retention of chlorides. This theory was also favored because of the diuresis which developed with restriction of salt and the normal excretion or even diuresis that occurred when water was given without salt. This only proves, according to Peters,^{30a} that water is not retained without an equivalent amount of salt. Furthermore, there is no direct evidence to indicate that the kidney is unable to excrete chlorides in nephritis, in fact, potassium chloride is well excreted. It has been shown in war edema and in famine edema and in edema caused by plasmapheresis in dogs, in none of which there is any real lesion of the kidney, that all the abnormal responses to salt, water and alkali may be produced which are found in nephrotic edema.³⁰ⁱ In other words, given a patient with a tendency to edema, that is, with serum proteins at or near the critical level, the amount of edema may be increased or decreased by varying the amount of salt ingested. This has been shown repeatedly.³⁰ In cases of hypoproteinemia with edema restriction of salt intake usually causes diuresis, and the edema may partially or completely disappear, depending to some extent on the level of the serum proteins. If the proteins are well below the critical level the edema will usually not disappear completely. If the proteins are at or above the critical level the edema may disappear completely. Likewise, so long as the serum proteins are at or near the critical level, relaxation of the restriction of salt intake will be followed by occurrence or increase of edema.

Whether the sodium or the chloride ion is more responsible for the production of the edema is a controversial point which will not be gone into in this paper. Peters^{30a} believed that the edema is not caused by the sodium or chloride per se, but by the provision of materials in the proportions in which they appear in interstitial fluids. The diuresis following production of hyperchloremia by acidifying diuretics such as ammonium chloride is due to a disturbance of the electrolytic pattern which the organism will not tolerate and hence diuresis is induced. Within certain limits the electrolytic pattern may be upset without causing diuresis, on the other hand, when the serum protein level is unusually

50 Albright, F, and Bauer, W. The Action of Sodium Chloride, Ammonium Chloride and Sodium Bicarbonate on the Total Acid Base Balance of a Case of Chronic Nephritis with Edema, *J Clin Investigation* 7 465, 1929. Liu, S H, Chu, H I, Li, R C, and Fan, C. Nutritional Edema. II Effect of Alkali and Acids on Nitrogen Balance, Plasma Proteins and Edema, *Proc Soc Exper Biol & Med* 29 252, 1931. Moore and Van Slyke¹¹ Weech and Ling¹⁸

low and hence the force that withdraws fluid from the interstitial spaces is weakened, an unusually great disturbance of electrolytes appears to be necessary to induce diuresis. In some of Peters' ³² cases, when the serum protein level was below 4 Gm per hundred cubic centimeters diuresis could not be induced by ammonium chloride, but after the protein level had risen above 4 Gm the chloride caused profuse diuresis.

TREATMENT OF HYPOPROTEINEMIA

It is apparent from the foregoing discussion that the most effective measure in treating edema associated with hypoproteinemia is a restriction of the intake of sodium chloride. If the serum proteins have fallen to what is commonly considered a critical level, that is, according to Moore and Van Slyke,¹³ the albumin to 2.5 Gm or below, or the total protein to 5.5 Gm or below, a potential hydropigenous state exists. Edema, if present, may often be eliminated without employing any procedure other than a limitation of the intake of sodium chloride. Likewise, relaxation of the restriction of salt will be followed by a prompt appearance or recurrence of the edema. This is especially important in some postoperative cases, especially those in which it has been necessary to operate in spite of a considerable degree of malnutrition. The patients with serum proteins at or near the critical level may be made quite edematous by a too zealous administration of physiologic solution of sodium chloride. In these cases, if edema is to be prevented, the salt should be restricted and the water balance maintained, principally by giving dextrose in 5 to 10 per cent solution intravenously or fluids by mouth or rectum, with little or no salt. This restriction of sodium chloride cannot be followed if contraindicated by oliguria or low plasma chloride. This type of postoperative edema is well illustrated in case 34, table 5, in which the patient had severe ulcerative colitis and repeated hemorrhages which made an ileostomy imperative. Postoperatively the serum proteins totaled 5.4 Gm and the serum albumin 2.24 Gm per hundred cubic centimeters. After receiving from 3,000 to 4,000 cc of physiologic solution of sodium chloride per day for two or three days the patient presented generalized subcutaneous edema, marked pulmonary edema and hydrothorax, which probably were factors in causing his death.

Acidifying diuretics such as ammonium chloride are also used in cases of hypoproteinemia with edema to promote diuresis. If, however, the total serum protein is below 4 Gm per hundred cubic centimeters neither the restriction of salt nor acidifying diuretics have much effect on the edema, and other measures such as transfusions or intravenous injections of acacia solutions must be resorted to in an attempt to raise the colloid osmotic pressure. In some cases of nephrosis in which the

serum proteins are not too greatly reduced feeding of a diet high in protein along with restriction of the salt intake may keep the patient free from edema. Although one can rarely bring low levels of total protein and albumin up to normal by a diet high in protein if there is not a spontaneous remission in the disease with a decrease in proteinuria, the total protein can usually be increased above the critical level, with a resulting disappearance of the edema, which is the most incapacitating feature of the disease. In the very severe cases of nephrosis, however, the loss of protein through the kidneys may equal or exceed the maximum rate of production of serum protein, so that no improvement can be obtained by a diet high in protein. As mentioned before, restriction of salt and acidifying diuretics have little or no effect in these cases in which the serum protein levels are very low. Transfusion may be used, and helps in some cases, but the transfused plasma albumin may be excreted in the urine almost quantitatively in a day or two. Hartmann⁵¹ advised use of acacia in a sufficient quantity to bring the colloid osmotic pressure up to or above the critical level in order to secure diuresis. This method is, no doubt, worthy of trial in severe cases, and is at times successful in bringing about a rise in the colloid osmotic pressure with resulting diuresis, thus ridding the patient of the edema and at the same time allowing the serum proteins to be increased by a diet high in protein. However, one must be cautious with this method, as Austin and McGuinness⁵² recently pointed out. The amount of acacia which must be given to bring the colloid osmotic pressure to a critical level when the serum proteins are very low is at times dangerous. Still more important perhaps, as Keith⁵³ pointed out, is that it should not be given in hypertonic but in physiologic solution of sodium chloride or in distilled water, since the hypertonic solution causes a dangerous increase in the volume of the plasma. In Austin's case of nephrosis with very low serum proteins the acacia produced diuresis and recovery from the edema, followed by a rise in the serum protein, but this occurred only after an initial period of alarming symptoms and a nearly fatal outcome. These symptoms were thought to be due to a marked increase in the volume of the plasma, and probably would not have occurred if the acacia had been given in physiologic instead of hypertonic solution (about 2 per cent) of sodium chloride.

It is well known that the serum protein level can be raised in most cases of nephrosis and the nephrotic type of glomerular nephritis by a

51 Hartmann, A. F., Senn, M. J., Nelson, M. V., and Perley, A. M. The Use of Acacia in the Treatment of Edema, *J. A. M. A.* **100**:251 (Jan 28) 1933.

52 Austin, J. H., and McGuinness, A. C. A Precaution Concerning the Treatment of Edema by Intravenous Administration of Acacia, *Tr. A. Am. Physicians* **48** 276, 1933.

53 Keith, N. M., in discussion on paper by Austin and McGuinness⁵².

diet high in protein. Various studies have shown that this same object can be accomplished in malnutritional and famine edema.⁵¹ However, the deficit in serum albumin disappears slowly with a diet high in protein, even though there is a positive nitrogen balance. This is no doubt due to the necessity of replenishing the wasted tissues before the blood proteins rise appreciably. In general, patients with hypoproteinemia of whatever cause should have at least 1 Gm of protein per kilogram of body weight, plus enough additional protein to counteract that lost by proteinuria in cases of nephrosis or by excessive metabolic destruction in cases of cachexia or malnutrition. In addition to this, there should be added from 5 to 20 Gm of protein to replenish the wasted tissues almost uniformly present.¹² The feeding of adequate protein to replenish the wasted tissues and to raise the serum protein level is not always easy, especially in cases of cachexia, because the frequently accompanying anorexia prevents an adequate intake. The carbohydrate intake should also be high in order that the proteins may be used as economically as possible. This is probably especially important in those cases of disease of the liver in which are also shown low levels of serum proteins. Although the usual cardiac edema is not due to decrease in serum proteins there are occasional cases of cardiac disease with very stubborn edema in which hypoproteinemia is also present and is probably a big factor in the edema. Chronic heart disease is a condition in which malnutrition may easily occur, and this should be guarded against by an adequate intake of protein.

SUMMARY

The occurrence of edema when serum protein levels are low is best explained on the theory of Starling, further elaborated by Govaerts and Shade and Clausen, that the colloid osmotic pressure, when lowered owing to a deficit in the serum protein, is unable to counterbalance the normal hydrostatic pressure and hence is unable to return sufficient fluid to the capillary bed, and edema results. Approximately 4 times as much colloid osmotic pressure is exerted by 1 Gm of albumin as by 1 Gm of globulin. For this reason the tendency to edema follows the level of the albumin more closely than that of the globulin or that of the total protein.

Epstein was the first to use this theory clinically in explanation of the edema in nephrosis. Edema associated with low serum proteins has been produced by feeding rats a diet deficient in protein. Low levels of serum proteins and edema have often been produced by plasmapheresis in dogs, that is, by bleeding, removal of the plasma and reinjection of the cells in saline or Locke's solution.

⁵⁴ Bruckman, D'Esopo and Peters²⁸ Liu, Chu, Wang and Chung¹⁹ Weech and Ling¹⁸ Youmans,²⁰ and Youmans, Bell, Donley and Frank²¹

Wai and famine edemas have been shown by several observers to be associated with an inadequate intake of protein and low levels of serum proteins

As to the site of the formation of plasma proteins, no evidence appears to be available except in the case of fibrinogen, which has been shown to be formed in the liver

Normally plasma contains from 6.2 to 8 Gm of protein per hundred cubic centimeters, of which from 3.6 to 5 Gm is albumin and from 2 to 3.5 Gm is globulin. The albumin-globulin quotient is from 1.2 to 2.2

Low levels of serum proteins and resulting edema may be found in a variety of clinical conditions and may be due to a number of causes such as (1) insufficient intake of protein due to an inadequate diet, (2) excessive loss of protein due to proteinuria, diarrhea or hemorrhage, (3) excessive metabolic wastage or destruction of protein due to chronic infections or cachectic states, (4) inadequate formation of proteins or decreased assimilation. The various clinical conditions in which low serum protein levels and edema appear owing to one of the aforementioned causes are discussed

As the serum protein levels fall, edema usually appears when the protein total reaches 5.5 ± 0.3 Gm per hundred cubic centimeters or when the albumin reaches 2.5 ± 0.2 Gm¹³. These are frequently called the critical levels since they are the levels at which edema usually appears and at which the hydropigenous tendency is most easily affected by other factors such as the intake of sodium chloride

Deficits of serum protein fall principally on the albumin fraction. The globulin fraction may be normal, decreased, increased slightly as a compensatory effort or increased markedly, especially when infection is present

The ratio of albumin to globulin is, in itself, probably of little or no importance, since an inversion of the ratio due to an increase in the serum globulin has a significance entirely different from that of an inversion due to a decrease in the serum albumin

The intake of sodium chloride and the electrolytic pattern have an important influence in modifying the edema associated with low levels of the serum proteins

Low levels of serum proteins, with resulting edema, are best prevented by adequate ingestion of protein. The best treatment is by a diet high in protein, restriction of sodium chloride intake and at times use of acidifying diuretics, transfusions of blood or plasma and intravenous administration of acacia

The cases cited in this paper were selected from the services of Dr G M Piersol and Dr H L Bockus

THE CARDIAC OUTPUT IN RELATION TO CARDIAC FAILURE

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A study of the cardiac output may be expected to throw light on the mechanism of the production of the clinical syndrome known as congestive heart failure. A number of such investigations have been made. Some authors¹ have reported a decrease in the cardiac output in patients with congestive heart failure. Others² have found the opposite, while still others have failed to observe any consistent change in this function³. The validity of these data is obviously dependent on the accuracy of the methods employed. Grollman⁴ pointed out that the methods used have been of doubtful reliability in patients with heart failure, and that the conclusions which have been arrived at by these procedures are therefore of questionable accuracy. Recently Grollman and his co-workers⁵ have defined criteria for determining the applica-

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2 Plesch, J. Hamodynamische Studien, *Ztschr. für exper. Path. u. Therap.* **6** 380, 1909. Eppinger, H., Kisch, F., and Schwarz, H. Das Versagen des Kreislaufes, Berlin, Julius Springer, 1927.

3 Kroetz, C. Messung des Kreislaufminuten volumens mit Azetylen als Fremdgas, *Klin. Wchnschr.* **9** 966, 1930. Kinamonth, J. G. The Circulation Rate in Some Pathological States with Observations on the Effect of Digitalis, *Quart. J. Med.* **22** 277, 1928.

4 Grollman, A. The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

5 Grollman, A., Friedman, B., Clark, G., and Harrison, T. R. Studies in Congestive Heart Failure. XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J. Clin. Investigation* **17** 751, 1933.

bility of methods for determining cardiac output to patients with cardiac disease, and a technic which appears to yield reliable results has been described. In our paper are presented data obtained by this method.

PROCEDURE

The subjects studied were hospital patients. They were trained to perform the rebreathing on one or more occasions prior to the beginning of the observations. Some patients experienced difficulty in breathing correctly and had to practice many times. Before and after the rebreathing procedures the basal oxygen consumption was measured by analysis of the expired air which was collected in a Tissot spirometer. The arteriovenous oxygen difference was determined by the acetylene method, the technic used being that described by Grollman and his associates.⁵ In this regard several points are worthy of emphasis.

If accurate results are to be obtained it is necessary that the rebreathing bag be emptied completely at each inspiration and that the expirations be maximal. The breaths not only should be of the greatest possible depth but should be rapid, each complete cycle lasting not more than two seconds.

The most satisfactory results are obtained when the gas mixture at the end of thirty seconds of breathing contains from 13 to 16 per cent oxygen and from 10 to 15 per cent acetylene. Such final concentrations can be approached in patients with cardiac disease if the original mixture contains from 24 to 28 liters of acetylene, from 0.7 to 1 liter of oxygen and sufficient air to make a total volume of 5 liters. These concentrations of oxygen and acetylene are greater than those recommended by Grollman for normal subjects. If the usual mixture is employed in patients with cardiac disease, the relative increase in the residual air, the smaller volume of gas in the bag and the prolongation of the rebreathing tend to produce final concentrations of both oxygen and acetylene which are too low for satisfactory results. It is best to determine the optimal gas mixture for each subject in preliminary tests, since different patients show considerable variations.

If accurate results are to be obtained it is necessary that at least three samples be taken, and that the arteriovenous difference as determined from the first and second samples be within 10 per cent of that calculated from the second and third. The first sample should be taken at from twenty to twenty-three seconds and the second and third at about four second intervals thereafter. Ordinarily in patients with congestive heart failure a complete mixture in the lung-bag system is not obtained in less than twenty-one seconds, and recirculation occurs at thirty seconds or very shortly thereafter. One therefore has only a narrow margin, and in many instances in which the breathing appears to be entirely satisfactory the criteria are not fulfilled and the results have to be discarded. At the first observation on a given subject it is helpful to take four samples, at twenty, twenty-four, twenty-eight and thirty-two seconds. From the arteriovenous oxygen differences calculated from each adjacent pair one can usually determine the approximate times at which mixing and recirculation occur and take the samples at subsequent observations accordingly. As patients recover from congestive heart failure it is usually preferable to take the samples a few seconds earlier.

In addition to measuring the cardiac output by the acetylene technic, we have determined this function in certain patients by the venous plateau procedure,⁶ which

6 Friedman, B., Clark, G., and Harrison, T. R. Studies in Congestive Heart Failure. XXII. A Method for Obtaining "Mixed" Venous Blood by Arterial Puncture, *J. Clin. Investigation* **13** 533, 1934.

is a modification of the method described by Burwell and Robinson⁷ for obtaining "mixed venous blood." In a previous communication⁵ it was shown that the venous plateau and the acetylene methods yield similar results when they are properly applied. The fact that our findings have been checked by two methods which are based on different principles, each of which has been critically tested against various sources of error, appears to offer convincing evidence of their validity.

Following the rebreathing procedure and the second determination of the oxygen consumption the vital capacity was measured.

The patients studied had various types of cardiac disease. Congestive failure⁸ was present in some and absent in others, and a number were studied both when suffering from and when free from failure with congestion. The subject received the usual treatment and the effect of the various therapeutic measures was investigated. These studies will be reported later. In the present report our interest has been centered on an analysis of the relation of the clinical state of the patient to the cardiac output and its related functions.

Control studies have been made on a series of patients without cardiac disease. In these cases the technique employed was similar to that which has been described, except that oxygen samples when the acetylene method was used, and the blood samples when the venous plateau procedure was employed, were drawn a few seconds earlier for in such cases mixing and recirculation occur sooner than in patients with cardiac disease.

RESULTS

The findings in the patients without cardiac disease are shown in table 1. The data are arranged in order from the highest to the lowest cardiac output per minute per square meter. The first three patients, who had overactive hearts associated with secondary anemia and the last subject who had partial venous obstruction due to a mediastinal tumor, had circulatory disturbances but had no cardiac disease. The different patients showed rather wide variations in all the functions studied. The cardiac output per minute ranged between 5.4 and 2.6 liters per square meter of body surface the cardiac output per minute was within Grollman's normal range (2.2 ± 0.3 liters) in nine instances above it in four and below it in five. The arteriovenous oxygen difference, which is an inverse measure of the cardiac output in proportion to the metabolic needs of the body, was on the average somewhat greater than in Grollman's normal subjects, being 70 cc or more per liter in four of the eighteen cases. This group of miscellaneous patients showed rather wide fluctuations in the various circulatory functions, but in

7 Burwell, C. S., and Robinson, G. C. A Method for the Determination of the Amount of Oxygen and Carbon Dioxide in the Mixed Venous Blood of Man, *J. Clin. Investigation* 1: 47, 1925.

8 This term as employed in our paper indicates the presence of dyspnea, edema, venous distention or hepatic engorgement in subjects at rest. In the strict pathologic implication the phrase means congestion, either systemic or pulmonary, dependent on cardiac disease. Restriction of the term to persons having systemic, as distinguished from pulmonary, engorgement seems to us unjustifiable.

TABLE 1—*The Cardiac Output of Patients Without Cardiac Disease*

Subject	Age	Sex	Diagnosis	Surface Area, Sq Meters	Weight, Lbs	Vital Capacity, per Sq Leters	Heart Rate	Oxygen Consumption per Minute, Ce	Basal Metabolic Rate, per Cent Normal	Arteriovenous Difference, per Liter, Cc	Cardiac Output per Minute, Leters	Cardiac Output per Sq Meter, Bant, Cc	Method Used for Testing Cardiac Output
F T *	48	M	Hodgkins disease, anemia	1.63	127	2.08	90	285	+11	37	4.9	3.05	51 Venous plateau
W H *	47	M	Glomerulonephritis, anemia	1.77	139	2.90	60	254	+10	48	5.4	3.02	90 Acetylene
J J *	45	M	Abdominal tumor, anemia	1.81	116	2.48	85	281	+18	53	5.3	2.92	62 Venous plateau
F D	28	M	Lead poisoning	1.75	140	3.08	68	242	— 1	52	4.6	2.64	68 Venous plateau
S T	60	M	Duodenal ulcer	1.77	143	2.69	73	218	+12	58	4.3	2.41	59 Venous plateau
E B	39	M	Chronic malaria	1.76	117	2.87	61	212	+ 2	79	4.1	2.11	64 Venous plateau and acetylene
B M	28	M	Nephrosis (receiving extract)	1.81	115	2.62	90	278	+11	67	4.1	2.40	46 Venous plateau and acetylene
F S	22	F	Diabetes mellitus	1.98	92	2.28	116	217	+23	69	3.2	2.29	28 Acetylene
T B	42	M	Syringomyelia	1.61	122	1.62	68	197	— 9	55	3.2	2.17	53 Acetylene
R G	38	M	Amebic dysentery	1.68	178	2.2	70	246	+12	71	3.6	2.14	51 Venous plateau
F G	26	M	Bronchial asthma (symptom free)	1.66	120	2.87	63	212	— 8	60	3.5	2.12	56 Venous plateau and acetylene
T A	18	M	Angioneurotic edema	1.77	113	2.03	70	208	+17	81	3.7	2.09	53 Venous plateau and acetylene
R C	16	F	Myoma of uterus	1.79	128	1.67	76	206	+ 7	67	3.1	1.93	10 Acetylene
I H	51	F	Unknown	1.88	110	1.88	101	168	+ 1	64	2.6	1.88	25 Venous plateau and acetylene
G P	53	M	Syphilis of the central nervous system	1.99	184	2.11	80	246	— 1	70	3.6	1.80	45 Venous plateau
B M	42	M	Optic neuritis	1.55	127	2.9	102	195	— 9	71	2.7	1.77	27 Venous plateau and acetylene
C Y	29	M	Syphilis of the central nervous system	1.71	148	2.45	68	187	—20	65	2.9	1.70	42 Venous plateau
R F *	33	M	Mediastinal tumor	1.61	147	1.99	76	218	— 8	95	2.6	1.62	54 Venous plateau and acetylene

* Possibly these cases should be omitted, for I T, W H and J J had circulatory disturbances dependent on increased metabolism and anemia, and R T had partial venous obstruction as the result of pressure by a mediastinal tumor

general the values were of the same general order as those found in normal persons.

The data on patients with cardiac disease are shown in table 2. Observations were made on twenty-seven patients who were free from symptoms at rest and on nineteen patients with congestive failure. Fifteen subjects were studied in both conditions. The findings on patients with congestive failure are presented last in the table, those on the patients who were studied only when free from congestive failure are shown first.

Of the patients without congestive failure nine had rheumatic heart disease, five had syphilis with aortic insufficiency, one apparently had syphilitic myocarditis and the remaining twelve had cardiac failure dependent on hypertension and/or arteriosclerosis. Within each etiologic group wide fluctuations were found in the values for cardiac output, and so far as can be judged from such a small series there appeared to be no correlation between this function and the underlying disease process. The eight patients with auricular fibrillation had cardiac outputs which were on the average somewhat less than those of the other patients without congestive failure, but the difference was not striking.

Of the patients with congestive failure five had rheumatic, four syphilitic and ten vascular cardiac disease. Again the values for the cardiac output appeared to bear little or no relation to the etiologic process. The five patients with auricular fibrillation had about the same cardiac output per square meter as the other subjects in the group.

Comparison of the data in table 1 with those in table 2 shows that the cardiac output per square meter of the patients with cardiac disease was as a rule less than that of the control subjects. There was considerable overlapping, however, and four of the latter subjects had a lower cardiac output per square meter than the average value for the patients with congestive heart failure. Likewise, in seven of the twenty-seven patients with cardiac disease but without congestive failure, and in seven of the nineteen subjects with congestive failure, the cardiac output per square meter was above Grollman's lower normal limit (1.9 liters). The arteriovenous oxygen differences of the patients with cardiac disease were in general greater than in the control subjects, but here again considerable overlapping occurred.

Of especial interest is a comparison between the persons with cardiac disease but with no symptoms at rest and the subjects with congestive failure. A summary of the results in these two groups, in our control subjects and in a series of healthy young adults studied by Grollman is shown in table 3. It can be seen that the range of the cardiac outputs and the average values for this function were similar in the "compensated" and "decompensated" patients. The arteriovenous oxygen difference was on the average, about 5 per cent higher in the latter subjects.

TABLE 2—The Cardiac Output of Patients with Cardiac Disease

Subject	Age	Sex	Diagnosis	Surface Area, Sq Meters*	Dyspnea†	Edema	Weight, Lbs	Vital Capacity per Sq Meter, Liters	Oxygen Consumption per Minute, Ce	Basal Metabolic Rate, per Cent Normal	Arteriovenous		Cardiac Output per Minute per Sq Meter, Liters	Cardiac Output per Beat, Ce	Method Used for Testing Cardiac Output	
											Oxygen Con	Difference				
L N	27	F	Mitral stenosis auricular fibrillation	1.49	+	0	111	1.41	80	230	+22	83	2.8	1.88	38	Acetylene
U R	39	M	Mitral stenosis auricular fibrillation	1.69	+	0	130	1.51	77	208	— 9	77	2.7	1.60	35	Acetylene and venous plateau
B G	34	F	Mitral stenosis	1.52	+	0	116	1.81	76	199	+ 1	76	2.6	1.73	34	Acetylene
E J	23	F	Aortic stenosis	1.38	+	0	92	1.81	61	193	+ 0	63	3.0	2.21	19	Acetylene
M S	39	F	Syphilitic aortic insufficiency	1.62	+	0	125	1.88	77	204	+ 2	66	3.2	2.00	43	Acetylene and venous plateau
T D	43	M	Syphilitic aortic insufficiency	1.67	+	0	137	1.53	63	221	+ 3	91	2.4	1.11	38	Acetylene
M B	75	M	Hypertension	1.85	+	0	163	1.57	78	242	+ 1	77	3.2	1.73	33	Acetylene
R O	29	M	Hypertension	1.54	+	0	136	1.79	82	187	— 5	68	2.7	1.75	39	Acetylene
P T	44	F	Hypertension	1.85	++	0	176	1.21	81	249	+ 10	76	3.3	1.79	39	Acetylene
J M	53	M	Arteriosclerosis	1.80	++	0	148	1.67	80	249	— 1	82	2.7	1.70	33	Venous plateau
L B	60	M	Arteriosclerosis	1.79	+	0	151	1.95	77	231	+ 3	70	3.3	1.91	14	Acetylene
P N	73	M	Arteriosclerosis	1.81	+	0	162	2.23	78	262	+ 11	69	3.8	2.10	65	Acetylene
A H	57	M	Hypertension, auricular fibrillation	1.78	+++	+	160	1.35	77	259	+ 15	72	3.6	2.02	47	Acetylene
C W	49	M	Hypertension	1.73	++	+	159	1.74	62	240	+ 3	81	3.0	1.68	48	Acetylene
M Y	72	M	Arteriosclerosis	1.47	++	+	111	1.63	74	173	— 2	51	3.1	2.30	16	Acetylene and venous plateau
A A	41	M	Arteriosclerosis	1.97	+++	+	173	1.45	76	282	+ 8	82	3.1	1.72	17	Burwell and Robinson

but this difference cannot be regarded as significant in view of the wide range of this function in both groups. On the other hand the basal metabolic rate, although exhibiting wide fluctuations within each group, was on the average about 15 per cent higher in the patients with congestive failure than in the other subjects with cardiac disease, and the average value for the vital capacity was 30 per cent higher in the latter group. The average cardiac output per beat was about 10 per cent greater in the patients without than in those with congestive failure,

TABLE 3—*Summary of the Values for the Cardiac Output and Related Functions in Persons with and without Congestive Heart Failure*

Group	Number of Subjects	Basal Metabolic Rate, per Cent Normal			Cardiac Output per Minute per Sq. Meter, Liters			Arteriovenous Oxygen Difference per Liter, Cc			Cardiac Output per Beat, Cc			Vital Capacity per Sq. Meter, Liters		
		Highest	Lowest	Mean	Highest	Lowest	Mean	Highest	Lowest	Mean	Highest	Lowest	Mean	Highest	Lowest	Mean
Normal subjects*	50				2.49	1.90	2.21	67	55	59	81	33	62			
Patients with out cardiac disease	18	+41	-20	+5 (+5)†	3.05	1.62	2.25 (2.15)	95	18	65 (65)	90	25	50 (52)	3.08	1.62	2.32 (2.20)
Patients with cardiac disease, with out congestive failure	27	+22	-20	+6 (+6)	2.51	1.03	1.72 (1.72)	132	60	80 (78)	66	25	42 (43)	2.23	1.00	1.64 (1.60)
Patients with congestive heart failure	19	+78	-9	+24 (+16)	2.56	1.37	1.85 (1.79)	108	51	81 (85)	60	16	35 (59)	1.74	0.77	1.27 (1.29)

* The values for the normal subjects were taken from Grollman's data.*

† The figures in parentheses denote the median values.

the values in both groups being less than in the control subjects without cardiac disease.

Fifteen patients were studied during congestive failure and, later, when free from symptoms at rest. As is shown in table 4, consistent alterations, i. e., changes of more than 10 per cent, were not noted in the cardiac output per minute or in the arteriovenous oxygen difference. However, in more than one half of the cases clinical improvement was associated with an increase in the stroke volume and with a decrease in the metabolic rate. The most consistent change occurred in the vital capacity, which increased by more than 10 per cent in thirteen of the fifteen cases and showed a slighter increase in the other two.

Observations concerning the ability of the heart to increase its work were made in three patients. Attempts to determine the arteriovenous oxygen difference during exercise resulted in failure, because recirculation occurs before mixing takes place in the majority of patients with congestive failure. However, the question can be studied in another way. The greater oxygen absorption which occurs during muscular exercise can be brought about by an increase either in the cardiac output or in the arteriovenous oxygen difference. However, the blood which

TABLE 4—*Changes in the Cardiac Output and Related Functions Following Clinical Improvement*

	Increase	Decrease	No Change*
Basal metabolic rate	1	8	6
Cardiac output per minute	3	7	5
Arteriovenous oxygen difference	4	6	5
Cardiac output per beat	9	3	3
Vital capacity	13	0	2

* No change means a change of 10 per cent or less

TABLE 5—*The Oxygen Consumption and Cardiac Output of Patients with Congestive Failure During the First Few Seconds of Exercise*

Subject	Diagnosis	Resting Values			During the First Few Seconds of Exercise			Type of Exercise
		Arterio-venous Oxygen Difference per Liter, Cc	Oxygen Consumption per Minute, Cc	Cardiac Output per Minute, Liters	Time of Collection of Expired Air, Seconds	Oxygen Consumption per Minute, Cc	Cardiac Output per Minute, Liters	
L W	Mitral stenosis, auricular fibrillation	80	212	2.6	3.10	249	3.1	Overventilation only
G M	Syphilitic myocarditis	78	251	3.2	5.15	500	6.4	Overventilation and rapid movement of arms and legs
F B	Syphilitic aortic insufficiency	109	265	2.4	2.10	643	5.9	Overventilation and movement of arms and legs
		113	279	2.6	5.10	631	5.6	

is in the veins and in the venous end of the capillaries at the beginning of exercise has already lost its quota of oxygen, and consequently the oxygen content of the mixed venous blood remains constant during the first few seconds of exercise. Since there is ordinarily no significant change in the oxygen content of the arterial blood, the arteriovenous difference in the lungs is the same as that in the previous resting state until the blood which was entering the capillaries at the start of the exercise reaches the lungs. Prior to this time the cardiac output changes directly as the oxygen absorption and may be calculated from measurements of the latter function at the onset of exercise and of the arteriovenous oxygen difference during the previous state of rest. Such

calculations are open to error because of the short period during which the oxygen absorption is determined, but they may be expected to reveal directional changes in the cardiac output

Observations made by this method are shown in table 5. Even if a relatively large error in the measurement of the oxygen consumption is assumed and even if some recirculation of blood occurred, the increase in oxygen absorption was of such large magnitude in two of the three patients that it can be ascribed only to a marked increase in the cardiac output. It is evident that even in the presence of congestive heart failure the myocardial reserve is not exhausted, although it is probably much diminished.

These data may be summarized as follows:

1. The cardiac output per minute per square meter of patients with congestive failure is usually lower than that of persons without cardiac disease, but may be within the normal range.

2. A similar diminution is found in persons with cardiac disease who are free from congestive phenomena. Whether groups are compared or the same person is studied before and after clinical improvement, constant changes in the cardiac output per minute are not found. The disappearance of congestive failure may be associated with an increase, a decrease or no change in this function. The arteriovenous oxygen difference, which is an inverse measure of the cardiac output in proportion to the metabolism, likewise exhibits no constant changes. The output of the heart per beat usually increases as clinical improvement occurs.

3. The oxygen absorption per minute is increased in certain patients with congestive failure and in such instances it usually decreases with improvement.

COMMENT

Two theories have been advanced concerning the mechanism whereby disorders of the heart produce the clinical manifestations of congestive failure. According to one hypothesis, which was clearly expressed a hundred years ago by James Hope,⁹ the phenomena are dependent on "back-pressure" from a dilated heart. This idea has been widely accepted by pathologists and is in general favor with European clinicians.

In the English-speaking countries the "backward failure" concept has been replaced in large measure by the "forward failure" theory, which attributes dyspnea and the other clinical manifestations of congestive heart failure to an inadequate supply of blood to the tissues as a result of exhaustion of the myocardial reserve.

⁹ Hope, James. *A Treatise on Diseases of the Heart*, American ed. 1, Philadelphia, Lea & Blanchard, 1842, p. 250.

Sir James Mackenzie,¹⁰ who was one of the chief proponents of this theory, stated

The symptoms of heart failure from deficient output of blood might be found in almost any organ did we possess the means of observing them. It so happens that one system which suffers early from an impaired blood supply is one which readily gives rise to distress. This is the respiratory system and it is the distress in breathing on response to effort which is usually the earliest sign of heart failure. As the heart failure proceeds the distress in breathing becomes more easily provoked until a stage is reached when it is present even when the body is at rest.

Sir Thomas Lewis¹¹ stated

Breathlessness is to be ascribed to a deficiency in the flow of aerated blood to the head and neck, at first the deficiency is confined to those exercises in which normally the cardiac output is much above resting values, at last there is a deficiency in the physiological quantity of aerated blood expelled by the heart while the body is at rest. It is when the output at rest declines that blood begins to collect on the venous side and the patient begins to manifest signs of congested veins and, associated with these, enlargement of the liver, cyanosis, a high-colored and scanty urine, ascites, dropsy of the lower members, and congestion and edema of the lungs.

Meakins and Davies¹² were of the same opinion.

We are pursuing further work on this question, but we would suggest that cardiac failure of this character is due to an incomplete ventricular systole as a consequence of which the circulation rate is greatly and progressively diminished until the amount of circulating blood is grossly insufficient to carry on the functions of the heart, kidneys, nervous system and other important organs.

Similarly, Meakins and Long¹³ said

Circulatory failure may be defined as a state in which the volume of blood circulated per unit of time is not adequate for the physical needs of the moment.

The same point of view has been expressed by American clinicians. Means¹⁴ stated

The fundamental fault responsible for cardiac dyspnea is obviously to be found not in the nature of the blood but the rate at which it is pumped, in the heart itself. The important point is that the heart either because of increased work, fatigue or degeneration is unable to maintain an adequate rate of blood flow.

Stewart and Cohn¹⁵ said

The volume output of blood per minute from the heart which is in failure is diminished and its size larger than when it is in a state of compensation.

10 Mackenzie, James. *Diseases of the Heart*, London, ed 4, 1925, p 33.

11 Lewis, Thomas. *Diseases of the Heart*, New York, The Macmillan Company, 1933, p 2.

12 Meakins and Davies,^{1b} p 319.

13 Meakins, J, and Long, C N H. *Oxygen Consumption, Oxygen Debt and Lactic Acid in Circulatory Failure*, *J Clin Investigation* 4 273, 1927.

14 Means, J H. *Dyspnea*, *Medicine* 3 309, 1924.

In a recent publication Blumgart and his co-workers¹⁵ wrote

It became apparent that circulatory insufficiency consists in the failure of the heart to maintain a blood supply adequate to the ordinary needs of the tissues at any given metabolic level

This point of view has been accepted by some physiologists as well as by clinicians. Thus, Henderson, Haggard and Dolley¹⁶ stated

The efficiency of the heart is nothing else than the volume of blood that it can pump in relation to the oxygen requirement of the body. This applies to the athlete, the man of sedentary habit and to the cardiac patient

It is evident from the foregoing quotations that the "diminished output" theory involves the following assumptions

1 The cardiac output per minute is subnormal in persons with congestive heart failure

2 Improvement in the clinical state is associated with an increase in this function

3 Diminution in the cardiac output—in proportion to the metabolic needs—necessarily results in an increase in the severity of congestive failure.

4 The presence of congestive failure indicates that the ability of the heart to increase its work has been lost ("The reserve has gone, the patient is breathless at rest, failure with congestion is beginning")¹⁷

The data which have been presented indicate that the first of these assumptions is true, in general at least. Although in some instances the cardiac output of persons with congestive failure may be within normal limits, it is usually decreased. It should be noted, however, that certain patients without circulatory disturbances may show a similar diminution.

On the other hand the data indicate that the further assumptions involved in the diminished output hypothesis are incorrect. Clinical improvement may be associated with an increase, a decrease or no change in the cardiac output per minute. Even in the presence of congestive failure the heart is able to increase its work, and its reserve power, although diminished, is not lost. It seems justifiable to conclude that the clinical manifestations of congestive failure are not essentially and primarily dependent on a diminished blood supply to the tissues.

15 Blumgart, H. L., Riseman, J. E. F., Davis, D. and Berlin, D. D. Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris, *Arch. Int. Med.* **52** 165 (Aug.) 1933

16 Henderson, Y., Haggard, H. W., and Dolley, F. S. The Efficiency of the Heart and the Significance of Rapid and Slow Pulse Rates, *Am. J. Physiol.* **82** 512, 1927

17 Lewis,¹¹ p. 157

Such a conclusion may seem rather surprising in view of the widespread acceptance of this theory. However, it is in accord with the results obtained by Hamilton, Moore, Kinsman and Spurling¹⁸ with their injection method. These authors found no consistent relationship between the cardiac output per minute and the degree of congestive failure. They reported decreased minute volume and stroke volume in the majority of their patients with congestive failure, some showed a cardiac output within normal limits, the disappearance of congestive failure was associated with no consistent alterations in the cardiac output. Using the same procedure, Weiss and Robb¹⁹ failed to find consistent abnormalities in the cardiac output in patients with cardiac asthma either during or between the attacks. The few patients with congestive failure studied by Lauter²⁰ by the direct Fick method showed subnormal cardiac output, but the same author found equally low values for this function in subjects without congestive manifestations and with normal tolerance for exercise.

Concerning the validity of the alternate theory of heart failure we have no direct evidence. The fact that clinical improvement is almost regularly accompanied by an increase in the vital capacity,²¹ when coupled with the observations of Drinker, Peabody and Blumgart,²² who found that compression of the pulmonary veins of the cat led to diminished expansibility of the lungs, suggests that the changes in vital capacity occurring in persons with congestive failure are related to back pressure from the left side of the heart. The well known parallelism between the height of the venous pressure and the severity of

18 Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G. Studies on the circulation. IV. Further Analysis of the Injection Method and of Changes in Hemodynamics Under Physiological and Pathological Conditions, *Am J Physiol* **99** 534, 1932.

19 Weiss, S., and Robb, G. P. Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and the Syndrome of Left Ventricular Failure, *J A M A* **100** 1841 (June 10) 1933.

20 Lauter, S. Kreislaufprobleme, *Munchen med Wchnschr* **77** 593, 1930.

21 Peabody, F. W. Clinical Studies on the Respiration, *Arch Int Med* **16** 846 (Nov) 1915, **16** 955 (Dec) 1915, **20** 433 (Sept) 1917. Peabody, F. W., and Wentworth, John A. Clinical Studies of the Respiration, *ibid* **20** 443 (Sept) 1917. Peabody, F. W., Wentworth, J. A., and Barker, B. I. Clinical Studies on the Respiration, *ibid* **20** 468 (Sept) 1917. West, Howard F. Clinical Studies on the Respiration, *ibid* **25** 306 (March) 1920. Peabody, F. W., and Sturgis, C. C. Clinical Studies of the Respiration, *ibid* **28** 501 (Nov) 1921. Sturgis, C. C., Peabody, F. W., Hall, F. C., and Fremont-Smith, F. Clinical Studies on the Respiration, *ibid* **29** 236 (Feb) 1922. Peabody, F. W., and Sturgis, C. C. Clinical Studies on the Respiration, *ibid* **29** 277 (March) 1922.

22 Drinker, C. K., Peabody, F. W., and Blumgart, H. L. The Effects of Pulmonary Congestion on the Ventilation of the Lungs, *J Exper Med* **35** 77, 1922.

congestive failure is likewise in accord with the "backward failure" hypothesis. In our study observations of venous pressure were not made, but the vital capacity (in contrast to the cardiac output) was found to exhibit consistent alterations as the clinical condition changed.

The results which have been obtained by the injection method are in accord with the "backward failure" theory. Hamilton, Moore, Kinsman and Spurling¹⁸ found that the disappearance of congestive failure was associated with a decrease in the volume of blood in the heart and lungs. In their patients with cardiac asthma Weiss and Robb¹⁹ reported an increase in the degree of pulmonary congestion as the most characteristic functional change during the attack.

Probably the most significant evidence in favor of the "back pressure" theory is to be encountered at the necropsy table. The majority of patients dying with cardiac failure show abnormalities of both sides of the heart and have congestion in both the pulmonary and systemic vascular beds. However, edema and congestion of the lungs, when occurring alone, are found in conjunction with lesions of the left side of the heart, whereas congestion and edema limited to the systemic circulation are encountered in persons with disorders of the right side. Cases illustrating the clinical picture produced by the failure of only one side of the heart have been reported by Robinson and Burwell.²³

Is there any evidence against the validity of the "backward failure" hypothesis? Certain authors²⁴ believe so, their observations being based on the idea that this theory involves the assumption of regurgitation through the auriculoventricular valves. However, a rise in pressure in the auricles may take place without leakage through these orifices. The investigations of Starling and his co-workers showed that dilatation is the physiologic response of the heart to an increase in work, injury, fatigue or a decrease in its supply of oxygen. When produced by fatigue, dilatation is associated with less complete systolic discharge and with an increase in the residual blood. The walls of the heart are distensible, but their distensibility is limited, and as they become stretched beyond a certain point a greater force is required to produce further stretching. When dilatation of the ventricle has reached this point, residual blood accumulates in the auricle until the pressure gradient between the two cavities has been reestablished at a higher level. Hence, dilatation of the ventricle, if of sufficient degree, may offer resistance to its diastolic filling. Under such conditions blood accumulates in the auricle, and when the latter chamber becomes sufficiently distended the intra-auricular pressure and venous pressure increase. During the

²³ Robinson, G. C., and Burwell, C. S. A Mechanism of Heart Failure, *Trans. Am. Physicians* **43**:49, 1928.

²⁴ MacKenzie¹⁰ and Lewis¹¹

period in which residual blood accumulates in the cavities the cardiac output is necessarily decreased by perhaps a few cubic centimeters per day. If by "diminished output" one means such a sequence of events, the hypothesis is correct. Actually, however, the theory has been held to imply a progressive diminution in the supply of blood to the tissues as congestive failure develops, and an increase in the blood supply with improvement. The data which we have presented show that the "diminished output" theory, when applied in this connection, is erroneous.²⁵

Similarly, the "back pressure" theory is probably incorrect if it postulates regurgitation through the auriculoventricular valves. However, if it is employed to indicate a rise in pressure in the veins "back" of the failing cardiac chamber as a result of dilatation and consequent resistance to inflow, the available evidence appears to support the theory.

The following description of the mechanism of congestive heart failure, which was written by James Hope⁹ a century ago, appears to be applicable at the present time.

As an obstacle to the circulation operates on the heart in a retrograde direction, the cavity situated immediately behind it is the first to suffer from its influence. Accordingly, all the impediments seated in the aorta, its mouth, or the arterial system, act primarily on the left ventricle, which being likewise exposed to the heaviest burden when the circulation is accelerated, has to conflict against a greater variety of exciting causes of hypertrophy than any cavity of the heart. On this account, therefore, as well as from the thickness of its parietes, it is subject to hypertrophy in a greater degree than any other.

So long as the left ventricle is capable of propelling its contents, the corresponding auricle, being protected by its valve, remains secure. Hence, in a large proportion of cases, the auricle is perfectly exempt from disease, while the ventricle is even enormously thickened and dilated. But when the distending pressure of the blood preponderates over the power of the ventricle, its contents, from not being duly expelled, constitute an obstacle to the transmission of the auricular blood. Hence the auricle becomes over-distended, and the obstruction may be propagated backwards through the lungs to the right side of the heart, and there occasion the same series of phenomena. When the obstruction thus becomes universal, as is frequently the case, it may either happen that all the cavities are thickened, or those only which, from their conformation, have the greatest predisposition to it.

25 In order to avoid misunderstanding, this statement should be amplified. In patients with acute cardiac failure such as occurs, for example, in coronary thrombosis, diphtheritic myocarditis and in certain instances of paroxysmal tachycardia, the phenomena of circulatory collapse (weakness, unconsciousness, thready pulse, diminished blood pressure, etc.) are in all probability to be ascribed to the diminution in cardiac output, for these manifestations occur in other types of acute circulatory failure in which the cardiac output is diminished, such as hemorrhage. However, the congestive phenomena, i. e., diminished vital capacity, râles at the bases of the lungs and dyspnea (the results of failure on the left side) and venous distention, hepatic engorgement and edema (the results of failure on the right side), are not related to a diminution in the supply of blood to the tissues, but appear to be dependent on increased pulmonary and systemic venous pressure.

When the mitral orifice is contracted, especially if the aperture be very small, the left ventricle, being insufficiently supplied with blood, is not stimulated to its ordinary contractile action, and consequently becomes emaciated and occasionally flaccid or softened. Meanwhile, the left auricle, having to struggle against the contracted valve in front, and also to sustain the distending pressure of the blood flowing in from the lungs, invariably becomes thickened and dilated. The engorgement, extending backwards through the lungs to the right ventricle, often occasions its hypertrophy and dilatation, under which circumstances, namely, hypertrophy of the right ventricle and contraction of the mitral valve, the lungs suffer in a preeminent degree for, being exposed to the augmented impulsive power of the right ventricle behind, and incapable of unloading themselves on account of the straitened orifice in front, their delicate and ill-supported vessels are strained beyond the power of resistance. If, therefore, they cannot disgorge themselves sufficiently by a copious secretion of watery mucus, they effuse blood by transudation into the air-vesicles and tubes, and form the disease denominated *pulmonary apoplexy*. I have found this affection to occur more frequently under the circumstances described, namely, great contraction of the mitral valve, with or even without, hypertrophy and dilatation of the right ventricle, than under any other.

When the mitral orifice is permanently patescent, so that, at each ventricular contraction, blood regurgitates into the auricle, this cavity suffers in a remarkable degree for it is not only gorged with the blood which it cannot transmit, but, in addition, sustains the pressure of the ventricular contraction. Permanent patescence of the mitral orifice, therefore, constitutes an obstruction on the left side of the heart, and the effect of this, as of contraction of the orifices, may be propagated backwards to the right side. The regurgitation is always considerable when it renders the pulse small and weak.

When the impediment to the circulation is primitively seated in the lungs, the right ventricle, situated immediately behind them, is the first to experience its influence, and when the cavity is so far overpowered by the distending pressure of the blood as to be incapable of adequately expelling its contents, the obstruction extends to the auricle,—the process being exactly the same as that which I have already described above, in reference to the left ventricle and auricle.

SUMMARY AND CONCLUSIONS

The cardiac output of patients with cardiac disease has been studied by the acetylene method, modified in such a way as to allow the detection of inaccurate results.

The cardiac output per minute of patients with congestive heart failure is usually from 10 to 30 per cent less than that of normal subjects, but may be within the normal range. Patients without circulatory disorders may have an equally low cardiac output. The level of the cardiac output per minute, whether considered as such or in relation to the metabolic rate, bears no relation to the presence or absence of congestive failure for

- 1 The range and the average values of the cardiac output are similar for compensated and decompensated patients.

- 2 In a given individual, clinical improvement and disappearance of congestive phenomena may be associated with an increase, a decrease

or no change in this function. In general, the output of the heart per beat tends to be somewhat less during congestive failure. The metabolic rate is normal in some patients and elevated in others.

These observations are interpreted as indicating that the "forward failure" (diminished output) hypothesis, which ascribes the clinical manifestations of congestive heart failure to an insufficient supply of blood to the tissues, is erroneous. The "backward failure" (back pressure) theory has been discussed and it is concluded that there is much evidence in favor of it and no valid evidence against it.

ANEMIA

CLASSIFICATION AND TREATMENT ON THE BASIS OF DIFFERENCES IN THE AVERAGE VOLUME AND HEMOGLOBIN CONTENT OF THE RED CORPUSCLES

M M WINTROBE, M D, P H D

BALTIMORE

The classification of anemia has never been satisfactory. Attempts have been made by various writers to classify the anemias according to the etiologic agents involved. While this is probably the most desirable method, a prerequisite is the discovery of the causative agent, which, in the light of the present inadequate knowledge and methods, is not always possible. From the therapeutic standpoint not only is it useful to know the cause of the anemia, but it is important to differentiate the anemias in accordance with the type of disorder in the hematopoietic system. Such a differentiation, however, is perhaps even more difficult at present than an etiologic classification.

As a consequence of this lack of a satisfactory classification, the differentiation in clinical practice of the various forms of anemia is, as a general rule, carried out in an inexact, haphazard manner. The discovery of the use of liver extract and the reemphasis of the value of large doses of iron preparations in the treatment of certain types of anemia have accentuated this confusion, for in the absence of clearcut methods of differentiation both liver extract and iron preparations have come to be employed without discrimination.

OBJECT OF THE PRESENT STUDY

The present studies were undertaken because it was thought that, if some relationship between morphologic differences in the red corpuscles and fundamental pathologic disturbances could be discovered, a useful classification of the anemias might be evolved.

Preliminary measurements¹ of the volume and hemoglobin content of the red corpuscles in patients with anemia indicated that it is possible to distinguish by these measurements four groups of anemia namely,

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1 Wintrobe, M M. Classification of the Anemias on the Basis of Differences in the Size and Hemoglobin Content of the Red Corpuscles, *Proc Soc Exper Biol & Med* **27** 1071, 1930

macrocytic, normocytic, simple microcytic and hypochromic microcytic (table 2) These groups did not exhaust all the possible variations in the number, size and hemoglobin content of the red corpuscles which form the basis of the classifications suggested by Osgood² and more recently by Haden,³ but represented the outstanding subdivisions

The preliminary observations have been pursued with several objects in view It was first necessary to determine how correct were the original impressions and how mutually exclusive were these types of anemia Again, it was important to discover, if possible, the relation between the type of anemia and the nature of the disturbance in the hematopoietic system Of interest in this regard would be the etiologic agents involved and the manner of response on the part of the hematopoietic system as determined by a detailed examination of the blood Finally, it was important to observe the nature of the changes which take place in the mean volume and hemoglobin content of the erythrocytes in each type of anemia in response to various kinds of treatment All this information would be useful in determining the practical value of the classification proposed

In pursuance of these objects several thousand examinations of the blood have been carried out on more than 1,000 persons under a variety of circumstances and during the course of various types of treatment The methods employed have already been described⁴

ACCURACY OF THE METHODS EMPLOYED

The accuracy of the methods employed was determined by repeated blood counts and hemoglobin and hematocrit determinations on single specimens of venous blood and on specimens of the same blood collected in several different vials The means, medians, standard deviations and coefficients of variation, with the probable errors, were calculated for each constant Eight experiments were carried out in this way.

The variations in the results of these examinations were small The mean of all the coefficients of variation for the red cell count was 0.64 per cent \pm 0.107, for hemoglobin, 0.9 per cent \pm 0.125, for volume of packed red cells, 0.59 per cent \pm 0.092, for mean corpuscular volume, 0.92 per cent \pm 0.092, for mean corpuscular hemoglobin, 1.07 per cent

2 Osgood, E. E. Hemoglobin, Color Index, Saturation Index and Volume Index Standards, *Arch Int Med* **37** 685 (May) 1926

3 Haden, R. L. Clinical Significance of Volume and Hemoglobin Content of the Red Blood Cell, *Arch Int Med* **49** 1032 (June) 1932

4 Wintrobe, M. M. (a) The Direct Calculation of the Volume and Hemoglobin Content of the Erythrocyte, *Am J Clin Path* **1** 147, 1931, (b) The Size and Hemoglobin Content of the Erythrocyte, *J Lab & Clin Med* **17** 899, 1932. (c) Macroscopic Examination of the Blood, *Am J M Sc* **185** 58 (Jan) 1933

± 0.12 , and for mean corpuscular hemoglobin concentration, 1.06 per cent ± 0.063

The greatest variation in each of the constants which can be attributed to the technic alone can be represented by the mean coefficients of variation plus 3 times their standard deviations. In no instance does this exceed 2.5 per cent. This value may therefore be considered the maximum variation attributable to technic.

THE VOLUME AND HEMOGLOBIN CONTENT OF THE ERYTHROCYTES IN NORMAL PERSONS

Data calculated from a number of carefully performed examinations of the blood are summarized in table 1. It will be seen that, on the whole, the mean values available for various localities are in agreement. The correspondence in the values for the two sexes is remarkably precise. The data available for persons over 30 years of age are inadequate, but they do not suggest that any significant change in the mean volume or hemoglobin content of erythrocytes occurs once adult life is reached. It appears, then, that the means of all the values recorded in table 1, namely, 87 cubic microns for mean corpuscular volume, 29 micromicrograms for mean corpuscular hemoglobin and 34 per cent for mean corpuscular hemoglobin concentration, may be employed as the mean normal values for healthy adults of either sex.

My experience suggests that the mean volume and hemoglobin content of the red corpuscles correspond rigidly during health to the pattern characteristic of the species. However, individual differences are encountered, and it is necessary to define, therefore, the limits of normal variation. I have chosen for this purpose my own recent determinations on 86 men and 101 women, because this represents a fairly homogeneous group of carefully selected persons.⁵ The frequency distribution of mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration in these persons is shown in chart 1.

As measured by the standard deviations recorded in chart 1, the mean volume of the red corpuscles would be ⁶ between 82 and 92 cubic microns in 85 per cent of normal persons, the mean corpuscular hemoglobin, from 27 to 31 micromicrograms in 88 per cent, and the mean corpuscular hemoglobin concentration, from 32 to 36 per cent in 86 per cent. The same data make it possible to estimate the likelihood that any given value is abnormal and in this way to *define microcytosis, macrocytosis and hypochromia*. The probability that a mean corpuscu-

⁵ Wintrobe, M. M. Blood of Normal Men and Women, Bull. Johns Hopkins Hosp. **53** 118 (Sept.) 1933.

⁶ Dunn, H. L. Application of Statistical Methods in Physiology, Physiol. Rev. **9** 341 (April) 1929.

lar volume of 79 cubic microns represents an abnormally low value (microcytosis) or that a volume of 95 cubic microns represents an abnormally high value (macrocytosis) is 49 1, and values of 75 and 99 cubic microns are, respectively, certainly indicative (1,999 1) of microcytosis

TABLE 1—Summary of Available Accurate Data on the Volume and Hemoglobin Content of Erythrocytes in Normal Blood*

Age	Locality	Authority	Men				Women			
			Number of Observations	Mean Corpuscular Volume, c μ	Mean Corpuscular Hemoglobin, $\gamma\gamma$	Mean Corpuscular Hemoglobin Concentration, %	Number of Observations	Mean Corpuscular Volume, c μ	Mean Corpuscular Hemoglobin, $\gamma\gamma$	Mean Corpuscular Hemoglobin Concentration, %
18 30	U S A , East	Wintrobe ⁵	60	86	29	34	70	87	29	34
18 30	U S A , Midwest	Haden ^{8†}	20	92	31	34	9	93	31	34
18 30	U S A , Midwest	Wintrobe ⁷	7	86	29	34	15	88	29	33
18 30	U S A , West	Osgood and Haskins (Arch Int Med 39 643 [May] 1927), Osgood ²	94	86	29	33	100	88	29	32
18 30	U S A , West	Wintrobe ⁵	2	87	29	33	3	88	30	34
18 30	U S A , South	Wintrobe (Proc Soc Exper Biol & Med 26 848, 1929, Arch Int Med 45 287 [Feb] 1930), Wintrobe and Miller (Arch Int Med 43 96 [Jan] 1929)	119	85	29	34	61	85	28	33
18 30	U S A , South	Foster and Johnson (Proc Soc Exper Biol & Med 28 929, 1931)	40	89	30	34				
18 30	Denmark	Gram and Norgaard (Arch Int Med 31 164 [Feb] 1923)	7	85	28	32	6	88	28	32
18 30	Denmark	Bie and Moller (Arch d mal du cœur 15 177, 1922)	10	84	27	32	10	82	28	34
Average for adults from 18 to 30 years of age			359	86 3	29 1	33 6	274	87 0	28 8	33 1
31 59	U S A , East	Wintrobe ⁵	5	85	29	34	20	86	29	34
31 59	U S A , Midwest	Haden ^{8†}	20	92	31	34	3	93	31	34
31 59	U S A , South	Wintrobe ⁵	4	84	28	33				
31 59	Denmark	Gram and Norgaard	3	85	28	33	4	86	28	33
Average for adults from 31 to 59 years of age			32	89 2	30 0	33 8	27	86 8	29 1	33 9
Over 60	U S A , East	Wintrobe ⁵	4	86	30	35	2	87	30	34
Average for adults of all ages			395	86 5	29 2	33 7	303	87 0	28 8	33 4
Average for 698 adults of all ages and both sexes				86 7	29 0	33 6				

* Only data for which adequate information is supplied as to the age and sex of persons examined are included. Investigations in which the methods employed may be questioned have been excluded. All values for volume of red cells are calculated to the volume in heparinized blood.

or macrocytosis. Likewise, the probability that the mean concentration of hemoglobin in the red corpuscles is abnormally reduced is great (37 1) when the concentration is 31 per cent, and hypochromia may be considered as certainly present (332 1) when the concentration is 30 per cent.

It should be stressed, however, that these statements are true only if the technic as outlined⁷ is rigidly followed.

7 Wintrobe, footnote 4 b and c

PHYSIOLOGIC VARIATIONS

In order to gain some background against which variations in the volume and hemoglobin content of erythrocytes occurring in association with various modes of treatment in the anemias can be interpreted,

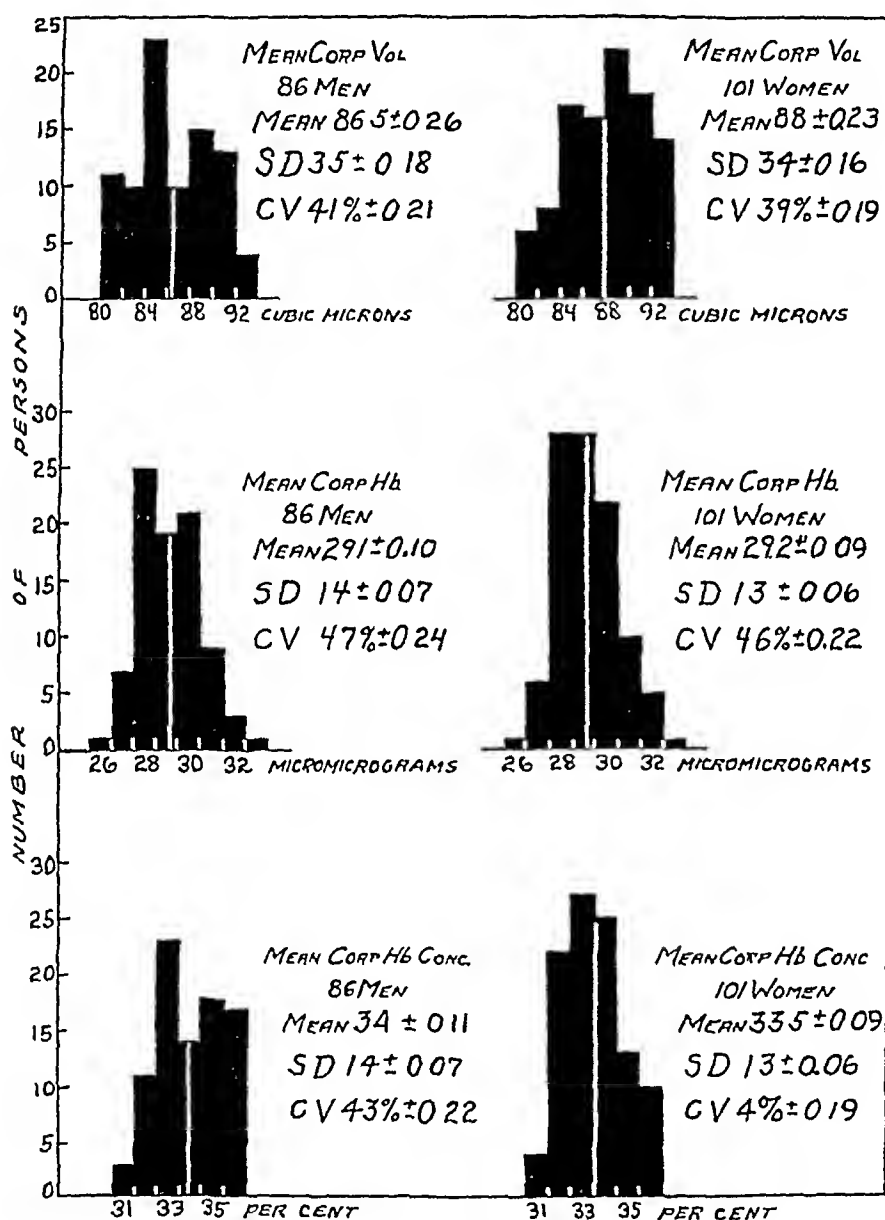


Chart 1—The mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration in 86 healthy men and 101 normal women. SD indicates standard deviation, CV, coefficient of variation. The position of the mean is indicated by the white line.

repeated examinations of the blood were made at one or two hour intervals in 10 persons and once a day for periods of from five to thirteen days in 8 persons. These groups included not only normal persons but also untreated patients with different illnesses and varying

degrees of anemia Variations in the conditions under which the blood was collected were arranged in order to imitate as far as possible the conditions of time, rest, exercise, taking of food and degree of anemia which are encountered in the majority of patients on whom studies of the blood are carried out

The results of these observations may be summarized by stating that *in normal persons* no fluctuations which were greater than could be attributed to technical variation were observed during a single day, but from day to day a slight variation, not exceeding 4.5 per cent, was noted These observations are in agreement with recent well controlled studies⁸ *In untreated patients with anemia* diurnal fluctuations which were beyond the limits of error were noted, and from day to day the variations were even greater There were individual differences in the degree of variation The maximum variation in mean corpuscular volume was from 6 to 7 per cent, in mean corpuscular hemoglobin from 7 to 8 per cent, and in mean corpuscular hemoglobin concentration from 5 to 6 per cent In most instances the variation was distinctly less than this

VARIATIONS IN THE VOLUME AND HEMOGLOBIN CONTENT OF ERYTHROCYTES IN DISEASE

To judge better the value of the morphologic classification of the anemias proposed in a preliminary report¹ the 464 cases of anemia which are here discussed have been separated arbitrarily in accordance with certain morphologic criteria⁹ All cases in which the mean cor-

8 (a) Rud, E. J. Le nombre des globules rouges chez les sujets normaux et leurs variations dans les diverses conditions physiologiques I L'influence de l'âge et du sexe sur le nombre des globules rouges, *Acta med Scandinav* **57** 142, 1922-1923, II Les variations du nombre des globules rouges dans les diverses conditions physiologiques, *ibid* **57** 325, 1922-1923 (b) Smith, C. Normal Variations in Erythrocytes and Hemoglobin Values in Women, *Arch Int Med* **47**:206 (Feb) 1931 (c) Smith, C., and Prest, M. Further Observations on the Normal Variations in Erythrocyte Values in Women, *Am J Physiol* **99** 562 (Feb) 1932 (d) Smith, C., and Kumpf, K. The Effect of Exercise on Human Erythrocytes, *Am J M Sc* **184**:537 (Oct) 1932 (e) Ponder, E., and Saslow, G. The Measurement of the Diameter of Erythrocytes VI The Diurnal Variation and the Effect of Exercise, *Quart J Exper Physiol* **20** 41, 1930 (f) Haden, R. L. Accurate Criteria for Differentiating Anemias, *Arch Int Med* **31** 766 (May) 1923

9 It will be observed that in the succeeding pages reference is made almost exclusively to the mean corpuscular volume and to the mean corpuscular hemoglobin concentration When these two constants are taken into account, little attention need be paid to the mean corpuscular hemoglobin, because alterations in the mean corpuscular hemoglobin tend to parallel those in the mean corpuscular volume, but are less marked than the latter Any differences between the two are indicated by alterations in the mean corpuscular hemoglobin concentration

puscular volume was greater than 94 cubic microns and the mean corpuscular hemoglobin concentration was 30 per cent or higher have been classed as macrocytic. The cases in which, in the presence of various grades of anemia, the mean corpuscular volume was between 80 and 94 cubic microns and the mean corpuscular hemoglobin concentration was 30 per cent or greater have been classed as normocytic. Those instances in which the mean corpuscular volume was less than 80 cubic microns and the mean corpuscular hemoglobin concentration was 30 per cent or higher have been placed in the simple microcytic group. All cases in which the mean corpuscular hemoglobin concentration was 29 per cent or less, whether the mean corpuscular volume was greatly or little reduced or even actually normal, have been classified as hypochromic. The values found when the patients were first seen, before any therapy was instituted, were taken as representative of the type of anemia present.

In table 2 the four types of anemia are schematically represented and their characters defined. In table 3 the clinical diagnoses in the cases showing the several types of anemia are recorded.¹⁰

Macrocytic Anemias—1 *Pernicious Anemia*. This is the outstanding example of the macrocytic type of anemia. I have previously described the characteristic alterations in the volume and hemoglobin content of the red corpuscles.¹¹ The observations previously recorded have been amply confirmed by subsequent studies in a larger number of cases. In table 4 correlation coefficients for all the observations on pernicious anemia are presented, and the regression coefficients for the mean corpuscular volume on the red cell count are recorded. It will be noted that these regression coefficients are somewhat different in the two sexes.^{4b}

2 *Other Conditions Associated with Glossitis and Diarrhea*. In several conditions in which glossitis and diarrhea were outstanding symptoms, macrocytic anemia was observed. The chief of these was non-tropical sprue. The changes in the blood in 8 such cases seen in Louisiana have already been reported.¹¹ Macrocytosis (mean corpuscular volume, 95 cubic microns, subsequently, 100 cubic microns) was also

¹⁰ It may be pointed out that the relative number of instances of the various types of anemia, and of the various diseases associated with them, does not, of course, represent their true incidence. Cases have been selected for study according to their interest, and there is therefore a great disproportion in their relative numbers.

¹¹ Wintrobe, M. M. Hemoglobin Content, Volume and Thickness of the Red Blood Corpuscle in Pernicious Anemia and Sprue, and the Changes Associated with Liver Therapy, *Am J M Sc* **181** 217, 1931. Wintrobe (footnotes 4b and 21).

found in 1 case of pellagra. In this case, concomitantly with the administration of a diet high in vitamins and especially supplemented with brewers' yeast, the anemia disappeared and the mean corpuscular volume returned to normal. A histamine test failed to demonstrate free hydrochloric acid in the gastric secretion.

In the 3 remaining cases of this group the changes in the blood were similar to those in pernicious anemia, but the clinical picture was

TABLE 2—*Morphologic Classification of Anemias*

Class and Severity	Number of Red Corpuscles	Mean Corpuscular Volume,	Mean Corpuscular Hemoglobin,	Mean Corpuscular Hemoglobin Concentration,	Description
		Vol * R B C	Hb * R B C	Hb * Vol	
Macrocytic Slight	—†	+	+	0	Red cells increased in volume, corpuscular hemoglobin proportionately increased, increase in size and hemoglobin content of red cells roughly inversely proportional to number of cells, corpuscular hemoglobin concentration remains normal throughout or may be slightly reduced
Moderate	— —	++	++	0 —	
Severe	— — —	+++	+++	0 —	
Normocytic Slight	—	0	0	0	Reduction in the number of red cells without any, or at most only a slight increase in mean corpuscular volume and mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration normal throughout
Moderate	— —	+ 0	+ 0	0	
Severe	— — —	+ 0	+ 0	0	
Simple microcytic Slight	—	0	0	0	Reduction in volume and hemoglobin content characteristically less marked than reduction in number of red cells, mean corpuscular hemoglobin concentration normal or only slightly reduced
Moderate	— —	—	—	0 —	
Severe	— — —	— —	— —	0 —	
Hypochromic microcytic Slight	0	—	— —	—	Reduction in volume and hemoglobin content characteristically more marked than reduction in number of red cells, mean corpuscular hemoglobin concentration characteristically reduced
Moderate	—	— —	— — —	— —	
Severe	— —	— — —	— — — —	— — —	

* Hb indicates the quantity of hemoglobin in grams per thousand cubic centimeters of blood, Vol, the volume of packed red cells in cubic centimeters per thousand cubic centimeters of blood, R B C, the number of red cells in millions per cubic millimeter.

† + denotes increase, — decrease, 0 no change from the normal, 0 — no, or only slight decrease and + 0 slight or no increase. The amount of increase or decrease is indicated by the number of plus or minus signs respectively.

unusual, the period of observation was short and a final diagnosis was not made. Liver therapy was attempted in only 1 of these cases. This was followed by clinical improvement, but only a slight decrease of the anemia occurred.

3 Disturbance of the Bone Marrow. In this group of 8 cases the average red cell count on admission was 2,120,000 and the average mean corpuscular volume was 102 cubic microns. In 1 of the cases of multiple myeloma the blood picture resembled that of pernicious anemia so closely

TABLE 3—*Clinical Diagnoses and Averages of Blood Values in 464 Cases of Anemia of Various Types*

Type of Anemia and Types of Cases Observed	Clinical Diagnosis in Observed Cases	Total No of Cases	Average Blood Values*			
			RBC	CV	CH	CHC
Macrocytic anemias			150			
1 Pernicious anemia	Pernicious anemia	94	2.58	108	37	34
2 Glossitis and diarrhea	Sprue (8), pellagra (1), undetermined (3)	12	2.71	112	36	33
3 Disturbance of the bone marrow	Multiple myeloma (2), earelnomatosis of bones (1), lymphosarcoma of the ilium (1), acute leukemia (2), sickle cell anemia (1), malignant neutropenia (?) (1)	8	2.12	102	35	34
4 Acute loss of blood	Peptic ulcer (3), abortion (2), familial angiectasia (1), scurvy (1)	7	2.25	90	31	31
5 Disorders of the liver	Cirrhosis (4), earelnoma (4), acute catar- rhal jaundice with achlorhydria (1), ars- phenamine jaundice (1), amyloidosis (1), syphilis (1), hepatomegaly of undeter- mined origin (6)	18	3.64	101	34	34
6 Pregnancy	Anemia with pregnancy	4	3.28	101	32	31
7 Miscellaneous	Earelnoma of the stomach (1), syphilis (?) of the stomach (1), abdominal pain of obscure origin (1), uremia (1), Addison's disease (1), malaria inoculata (1), perni- cious anemia (?) without achlorhydria (1)	7	3.53	101	33	33
Normocytic anemias			135			
1 Acute destruc- tion of blood (malaria)	Tertian malaria (8), estivo autumnal (3)	11	3.41	85	29	34
2 Acute loss of blood	Hemorrhage from the intestines (4), nose (3), hemorrhoids (1), uterus (1), hemo- philia (2), purpura (2)	13	3.38	84	29	35
3 Aplastic anemia	Idiopathic (5), following arsphenamine (1)	6	1.50	84	30	35
4 Disturbance of the bone marrow	(a) Leukemia chronic myeloid (10), chronic lymphoid (10), acute (8), mono- cytic (1) (b) Sickle cell anemia (4), multiple mye- loma (2), bone metastases from earel- noma of prostate (1)	29 7	3.38 3.20	86 84	29 28	34 34
5 Inflammatory diseases	Pneumonia (3), pulmonary abscess (2), chronic cholecystitis (2), chronic arthritis (2), pelvic inflammatory disease (1), infec- tion of the urinary tract (2), ileocolitis (1), typhoid myelitis (1), fever (?) (1), splenic thrombosis (1), neuritis (1), dermatitis (1)	18	3.88	87	29	34
6 Nephritis	Acute (2), subacute (1), chronic vascu- lar (4), uremia (2)	9	3.56	87	29	34
7 Chronic non- inflammatory diseases	(a) Malignant process (stomach, lung, kidney, lymphosarcoma) (8), Hodgkins (2), syphilis (2), pellagra (3), Addison's (2), myxedema (1), doubtful (2) (b) Disorder of the liver earelnoma (5), cirrhosis (4), arsphenamine jaundice (2), amyloidosis (1), unexplained (4)	20 16	3.96 3.94	88 88	30 28	34 32
8 Pregnancy	"Physiologic" anemia of pregnancy	6	4.19	88	27	31
Simple microcytic anemias			78			
1 Subacute and chronic in- flammatory diseases	(a) Pulmonary (tuberculosis, abscess, bron- chiectasis, bronchitis, empyema) (b) Pelvic (abscess, salpingitis, peritonitis, infection following abortion) (c) Arthritis (chronic, infectious) (d) Miscellaneous (tuberculosis of the mes- enteric glands, colitis, unexplained fever, perinephritic abscess, granuloma ingui- nale, rheumatic fever)	6 5 6 10	4.33 3.59 4.38 4.11	76 75 75 72	24 26 23 23	32 34 31 33
2 Nephritis	Chronic nephritis (16) with uremia (3)	19	3.60	75	25	33
3 Chronic non- inflammatory diseases	(a) Plumbism (b) Malignancy without loss of blood (c) Endocrine (Addison's, Simmonds', ex- ophthalmic goiter) (d) Miscellaneous (syphilis, rectal stricture, congenital hemolytic jaundice, etc.)	6 5 4 13	4.11 3.71 4.03 3.77	72 74 72 74	24 24 23 25	33 32 33 34
4 Pregnancy	"Physiologic" anemia of pregnancy	4	4.56	75	24	32
Hypochromic microcytic anemias			101			
1 Chronic loss of blood	(a) Malignant process with loss of blood (earelnoma of the stomach, intestines) (b) Intestinal hemorrhage due to other causes (hemorrhoids, portal cirrhosis of the liver with loss of blood, peptic ulcer, etc.) (c) Uterine (d) Other causes (purpura, papilloma of the bladder, telangiectasia)	11 17 16 10	3.61 3.66 3.14 3.63	72 70 71 72	21 19 20 21	28 28 28 28
2 Idiopathic	(a) "Idiopathic hypochromic anemia" (b) Associated with pregnancy (c) Miscellaneous with hypertension (2), arthritis (1), amyloidosis (1), chlorosis (?) (1), unclassified (5)	23 10 10	4.27 3.98 4.02	65 73 75	18 21 22	28 29 29
3 Hookworm infestation		4	3.00	69	18	25

* RBC, number of erythrocytes in millions per cubic millimeter, CV, mean corpuscular volume in cubic microns, CH, mean corpuscular hemoglobin in micromicrograms, CHC, mean corpuscular hemoglobin concentration in per cent

that this was the first diagnosis made. In addition to the atypical symptomatology it was noted, however, that there was no poikilocytosis and that the icterus index was normal. There was evidence of increased activity of the bone marrow, there being nucleated red cells, polychromatophilia and stippling, as well as a slight shift to the left in the leukocytes of the granular series. Following the institution of liver therapy a reticulocyte response occurred, but the erythrocyte count failed to rise (chart 2A).

In 5 of the remaining 7 cases of this group (table 3) the finding of an increased mean corpuscular volume was confirmed by repeated

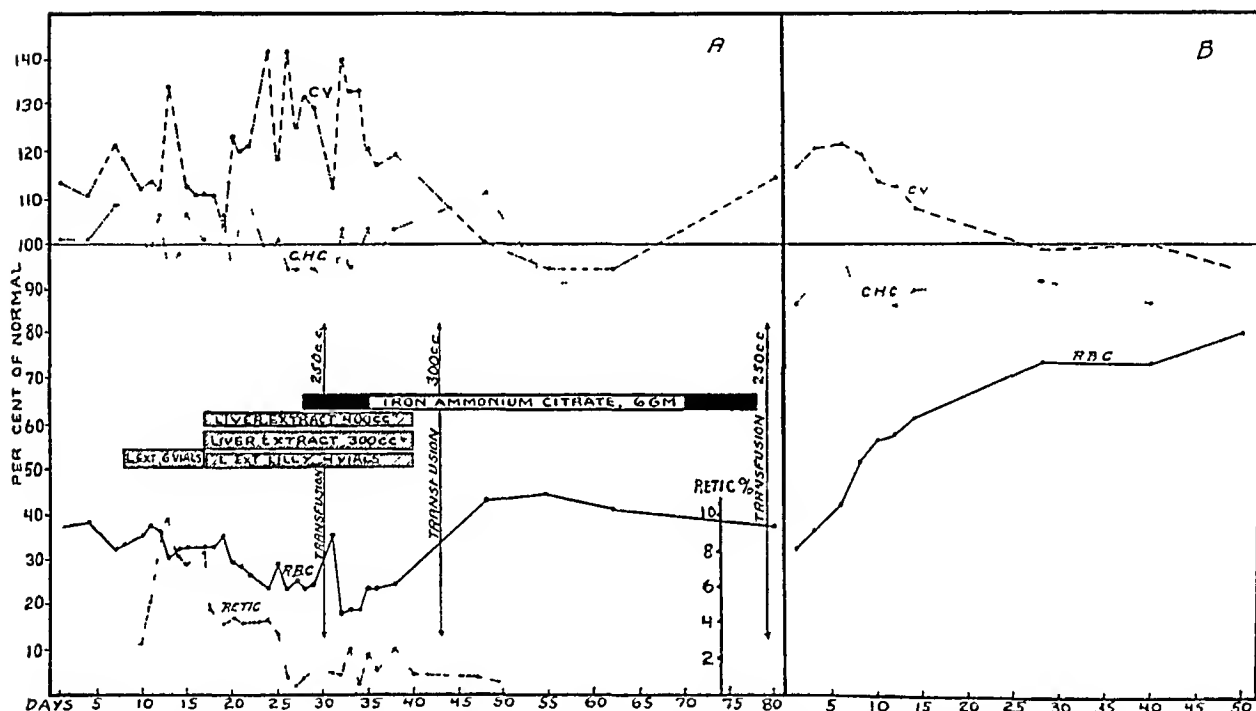


Chart 2—Macrocytic anemia. Variations in the mean corpuscular volume and in the mean corpuscular hemoglobin concentration in multiple myeloma (A) and in acute posthemorrhagic anemia (B). All values except those for reticulocytes are charted as percentages of the respective average normals. By this method the red cell count, the mean corpuscular volume, the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration of a hypothetical normal person would fall on the line at 100 per cent. RBC indicates red corpuscles, Retic, reticulocytes, CV, mean corpuscular volume, CHC, mean corpuscular hemoglobin concentration.

examinations. In the case of lymphosarcoma of the ilium and in the case of malignant neutropenia only one examination was made. The latter case was not typical of the Schulz syndrome and at autopsy there was evidence of widespread infection, focal necrosis of the liver and hyperplastic bone marrow. There was active blood formation (poly-

chromatophilia, etc) in the 6 cases in this group in which the erythrocyte count was below 3,000,000 Liver extract was given to 1 patient with acute leukemia and to the patient with sickle cell anemia, but no response occurred

4 Acute Loss of Blood The average erythrocyte count in these 7 cases (table 3) was 2,250,000, while the average of the mean corpuscular volumes was 99 cubic microns The highest mean corpuscular volume was 103 cubic microns The macrocytosis in these cases was thus distinctly less than is found in pernicious anemia In all the cases the macrocytosis was discovered within a few days following the loss of blood and before transfusion was given In the 5 cases in which the erythrocyte count was below 3,000,000 there was obvious evidence of increased activity in the bone marrow in the form of polychromatophilia and nucleated red cells, as well as a shift to the left of the myeloid leukocytes In 1 patient, who was allowed to recover spontaneously without transfusion, the macrocytosis gradually disappeared as the erythrocyte count rose (chart 2B)

5 Disorders of the Liver Eighteen cases of macrocytosis and macrocytic anemia associated with disorders of the liver have been observed These cases include a variety of hepatic diseases (table 3) The average erythrocyte count was 3,640,000, and the average of the mean corpuscular volumes 101 cubic microns The anemia in all these cases was relatively moderate The macrocytosis was as great as might have been expected in pernicious anemia Indeed, in 3 instances an increased mean corpuscular volume was found, although the erythrocyte count was within normal limits The occurrence of spontaneous remissions in the anemia in these cases, the influence of liver therapy and other details are discussed elsewhere¹²

6 Pregnancy In 1 of 4 instances of macrocytic anemia associated with pregnancy hypochromic anemia of unknown origin associated with achlorhydria changed during pregnancy to macrocytic anemia This case is described elsewhere¹³ In another case macrocytic anemia was associated during the fifth month of pregnancy with a fever of obscure origin The latter disappeared and subsequently the anemia became less marked and the size of the cells returned to normal In 2 other cases macrocytic anemia was observed near term, but in both instances it

12 Wintrobe, M. M., and Schumacker, H. S. The Occurrence of Macrocytic Anemia in Association with Disorder of the Liver, Together with a Consideration of the Relation of This Anemia to Pernicious Anemia, *Bull. Johns Hopkins Hosp* **52** 387 (June) 1933

13 Wintrobe, M. M., and Beebe, R. T. Idiopathic Hypochromic Anemia, *Medicine* **12** 187 (May) 1933

was moderate Liver was administered, but unfortunately the patients could not be followed up It is known that their course was uneventful

7 Miscellaneous In a case of carcinoma of the stomach slight anemia (red cell count 4,400,000) with macrocytosis (mean corpuscular volume, 99 cubic microns) was observed The patient died and no studies of the anemia could be made In a woman in whom the Wassermann reaction of the blood was positive, and who complained of vomiting after meals, and of weakness and sore tongue since the onset of the illness three months before, macrocytic anemia (red cell count, 3,040,000, mean corpuscular volume, 105 cubic microns) was found No further studies could be made In another patient 2 attacks of

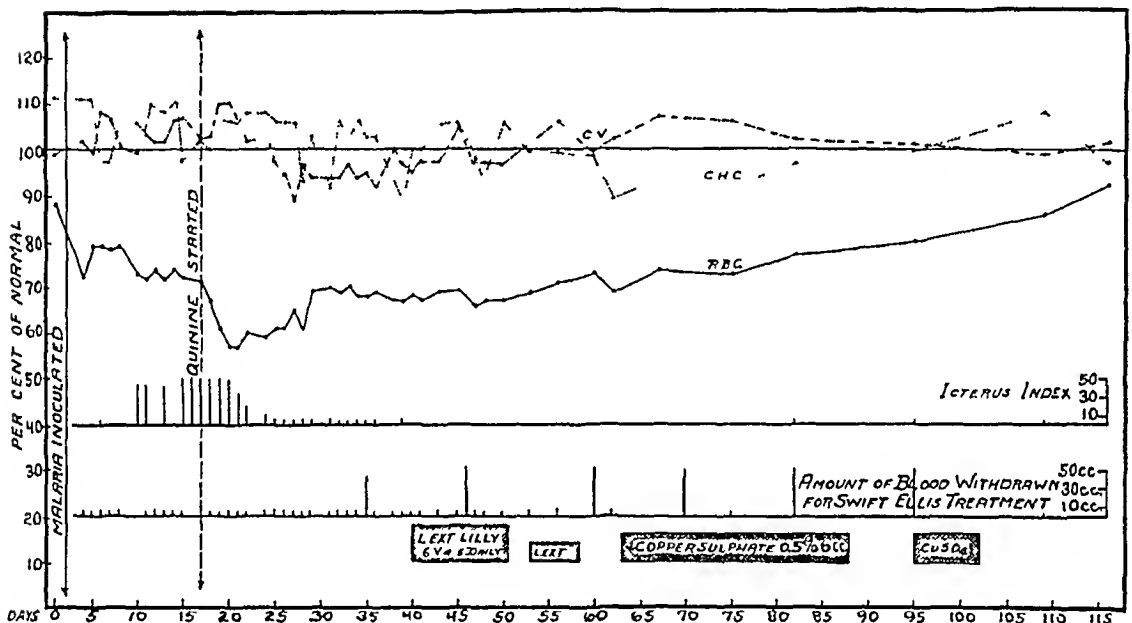


Chart 3—Normocytic anemia Variations in the mean corpuscular volume and in the mean corpuscular hemoglobin concentration in hemolytic anemia caused by malaria (tertian, inoculata)

abdominal pain were each time associated with the development of macrocytic anemia (red cell count, 3,290,000, mean corpuscular volume, 110 cubic microns) which disappeared spontaneously Exhaustive studies failed to reveal any abnormalities In a patient who died of uremia erythrocyte counts of 2,300,000 and 2,110,000 and mean corpuscular volumes of 100 and 109 cubic microns were found In the blood smear there were many macrocytes, marked poikilocytosis and some polychromatophilia The gastric juice contained free hydrochloric acid Autopsy was not performed, so that no further clue with regard to the cause of the anemia was discovered In a case of Addison's disease slight macrocytosis was repeatedly observed (red cell count, 4,030,000, mean corpuscular volume, 98 cubic microns) Gastric

analysis showed hypochlorhydria. In a case of malaria inoculata macrocytosis developed as the anemia progressed (red cell count, 3,840,000, mean corpuscular volume, 99 cubic microns), but gradually decreased as the red cell count rose, and finally disappeared a month later. The

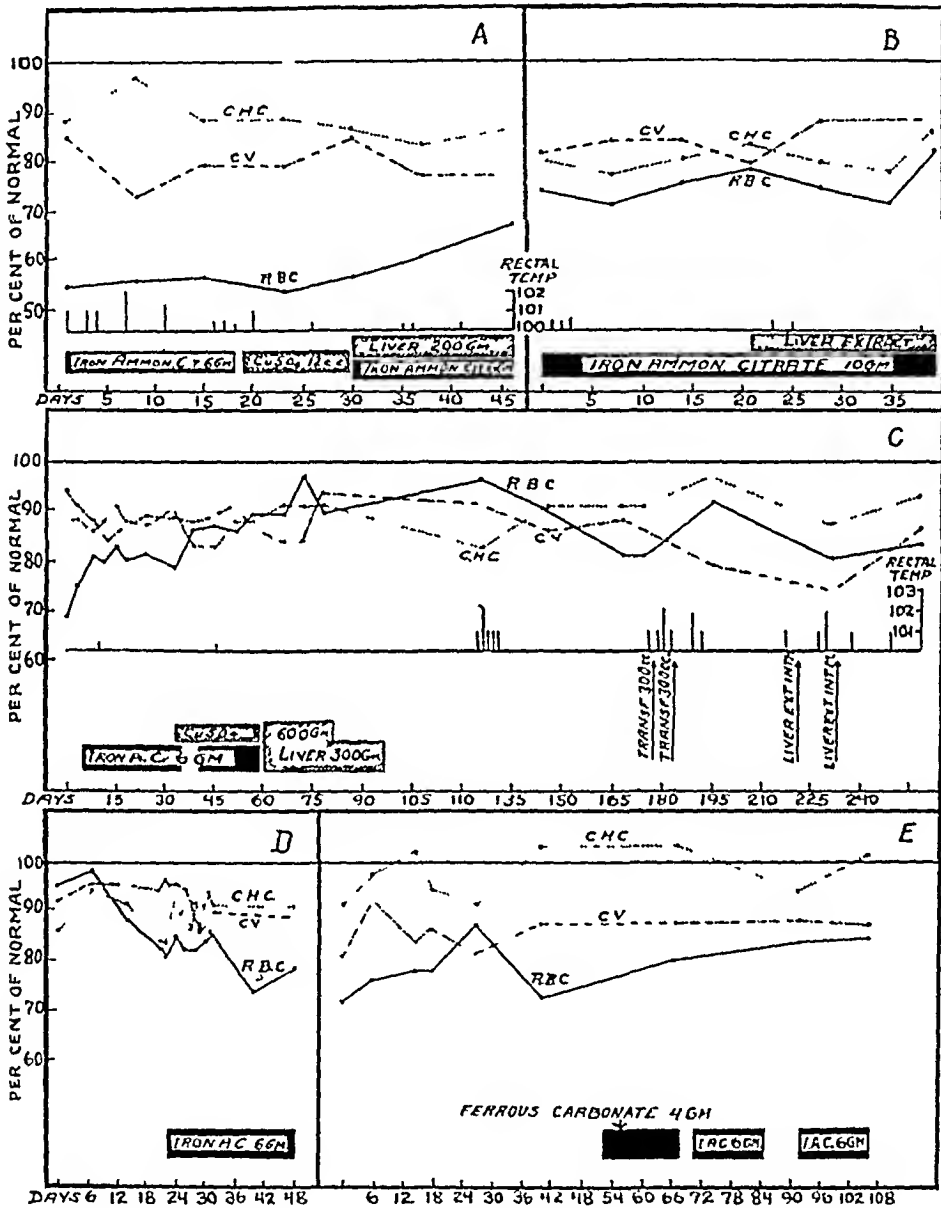


Chart 4—Simple microcytic anemia. Variations in the mean corpuscular volume and in the mean corpuscular hemoglobin concentration in a case of chronic infectious arthritis (A), empyema (B), tuberculosis of the mesenteric glands (C), chronic hemorrhagic nephritis (D) and lead poisoning (E).

last member of this miscellaneous group is still under observation. She may have pernicious anemia, although the gastric juice contains free hydrochloric acid.

Normocytic Anemias—1 *Acute Destruction of Blood (Malaria)* Three patients with estivo-autumnal malaria and 9 patients treated by the inoculation of tertian malaria have been studied. Six were observed over periods varying from eleven to thirty-three days and 1 for four months (chart 4). In the latter daily observations were made for fifty days. The anemia produced in these cases was never extremely severe, the lowest erythrocyte count being 2,910,000. Except in the 1 case already mentioned no variations occurred in the mean size or hemoglobin content of the erythrocytes which were beyond the limits of normal. The influence of liver extract and of copper was observed in only 1 case (chart 3). It is probable that the recovery from the anemia in this case was unrelated to the therapy and entirely spontaneous.

2 *Acute Loss of Blood* In 13 cases in which the anemia was due to acute loss of blood no significant alteration in the mean volume or hemoglobin content of the red cells was noted. The average red cell count was 3,380,000, the average mean corpuscular volume, 84 cubic microns, the average mean corpuscular hemoglobin, 29 micromicrograms, and the average mean corpuscular hemoglobin concentration, 35 per cent. Several of these cases were observed during recovery from the anemia, and no macrocytosis was found at any time. As a whole the anemia was less severe than in the group in which macrocytic anemia was observed, although there were 3 cases in which the erythrocyte count was below 3,000,000. It may be significant, however, that in none of these cases was there evidence of marked stimulation of the bone marrow.

3 *Aplastic Anemia* In 5 cases of idiopathic aplastic anemia, in spite of extreme anemia, no changes from the normal in the mean volume or hemoglobin content of the erythrocytes took place. The average red cell count in these cases was 1,480,000, the average mean corpuscular volume, 83 cubic microns, the average mean corpuscular hemoglobin, 30 micromicrograms, and the average mean corpuscular hemoglobin concentration, 35 per cent. Likewise, in a case of aplastic anemia caused by arsphenamine the mean size and hemoglobin content of the erythrocytes remained normal, although the erythrocytes fell to 1,580,000. Liver therapy was ineffective, but after a dramatic course, during which the patient contracted estivo-autumnal malaria and, when this had been successfully treated, had multiple abscesses in various muscles, regeneration of the blood took place after fifteen transfusions, and the patient recovered. During recovery the mean corpuscular volume rose to a maximum of 100 cubic microns.

4 *Disturbance of the Bone Marrow* In the leukemias the accurate determination of the volume of packed red cells, and consequently of

the mean corpuscular volume, is attended with some difficulty because of the great volume of leukocytes. However, in most instances, if the filled hematocrit is allowed to stand for several hours before centrifugation is carried out, satisfactory separation of the red and white corpuscles is attained.^{4c} In 29 cases of leukemia of various types (table 3), in which red cell counts as low as 1,320,000 were found, the volume and hemoglobin content remained consistently within the limits of normal value, even in the most extreme cases.

To this group of conditions, in which some form of disturbance of the bone marrow was present, may be added 4 cases of sickle cell anemia, 2 cases of multiple myeloma and 1 case in which metastases to bone from carcinoma of the prostate gland were found. The anemia in all these cases was associated with no alteration in the mean volume and hemoglobin content of the erythrocytes, and in the 3 cases last mentioned no evidence of increased activity of the bone marrow was found.

5 *Inflammatory Diseases* In these cases (table 3) the anemia was moderate, the lowest erythrocyte count of the group being 2,620,000 and the average 3,880,000. As in the other cases of normocytic anemia, although there were some differences in the mean volume and hemoglobin content of the erythrocytes in the various cases, these variations were all within the limits of the normal value.

6 *Nephritis* The lowest erythrocyte count in this group (table 3) was 2,910,000 and the average 3,560,000. The values for the mean volume and hemoglobin content of the erythrocytes were all well within normal limits. In several cases of chronic vascular nephritis treatment with liver or liver extract and with iron was attempted, but proved of no avail. In a case of acute diffuse glomerulonephritis prolonged treatment with iron was associated with a decrease of anemia, but it was impossible to determine whether this was due to the therapy or was simply associated with the abatement of the attack of nephritis.

7 *Chronic Noninflammatory Disease* Nothing of interest with regard to the anemia in these cases can be added to the data presented in table 3. The detailed examination of the blood in these patients revealed from slight to moderate anisocytosis and poikilocytosis, with no striking predominance of either microcytes or macrocytes and no evidence of increased erythropoiesis. In the majority of the cases the anemia was moderate, and in only 4 was the erythrocyte count below 3,000,000 cells.

8 *Pregnancy* In all the cases of anemia associated with pregnancy in which no significant alterations in the mean volume and hemoglobin content of the erythrocytes were found the anemia was slight (table 3).

Simple Microcytic Anemias—The changes in the blood in a variety of subacute and chronic ailments of inflammatory and noninflammatory

nature in which moderate microcytosis and little or no hypochromia were found are shown in table 3. The mean corpuscular volume in these cases ranged between 70 and 80 cubic microns. Rarely were smaller volumes observed. The mean corpuscular hemoglobin concentration ranged from 30 to 36 per cent. The details of the morphologic changes in this type of anemia are too well known to require elaboration. In a number of cases therapy was attempted, but iron and copper preparations, liver and various liver extracts seemed to be of equally little value as long as the cause of the anemia persisted (chart 4).

Hypochromic Microcytic Anemias—Anemia characterized by moderate or marked microcytosis and marked hypochromia was consistently found in three groups of cases, namely, those in which chronic loss of blood played a great rôle, an idiopathic group and cases of hookworm infestation. The changes in the blood in all these cases were essentially similar. In most instances the mean corpuscular volume was very low, many values ranged between 60 and 70 cubic microns, while a few were less than 60 cubic microns. The lowest value observed was 50 cubic microns. The mean corpuscular volume, however, was not always greatly reduced, the severity of the anemia and therapy apparently being controlling factors. In 2 exceptional cases, in which the anemia was severe (incomplete abortion, erythrocytes 1,040,000, hookworm infestation, erythrocytes 1,080,000), the mean corpuscular volume was not low, as would have been expected, but actually 96 and 92 cubic microns respectively. What seems to be the essential characteristic of the entire group of cases is marked hypochromia. The mean corpuscular hemoglobin concentration was frequently 27, 28 or 29 per cent, not unusually 25 per cent and in several cases as low as 21 per cent. Such low values were never observed in any of the other classes of anemia described here.

Examination of the blood smears in these cases revealed, in the severest cases, pale ringlike red corpuscles of all shapes and sizes. A few were unusually large, but the majority were microcytes. Poikilocytosis was marked. Occasionally a better filled, perhaps polychromatophilic red cell could be seen, and sometimes nucleated red cells, usually microblasts. The leukocytic picture varied, but frequently normal or reduced counts showing absolute granulocytopenia were found. Blood platelets were usually present in about normal numbers. In the less severe cases the changes in the blood smear were less marked, but pallor of the red cells was usually the most striking observation. The mean values in the several groups of cases are shown in table 3.

1 Chronic Loss of Blood. Little need be added concerning the anemias resulting from chronic loss of blood except in regard to their

response to treatment. In the cases associated with malignant processes the response to treatment either with liver or liver extracts or with iron was usually poor (chart 5B and C), although sometimes a decrease in the anemia took place under treatment with iron preparations (chart

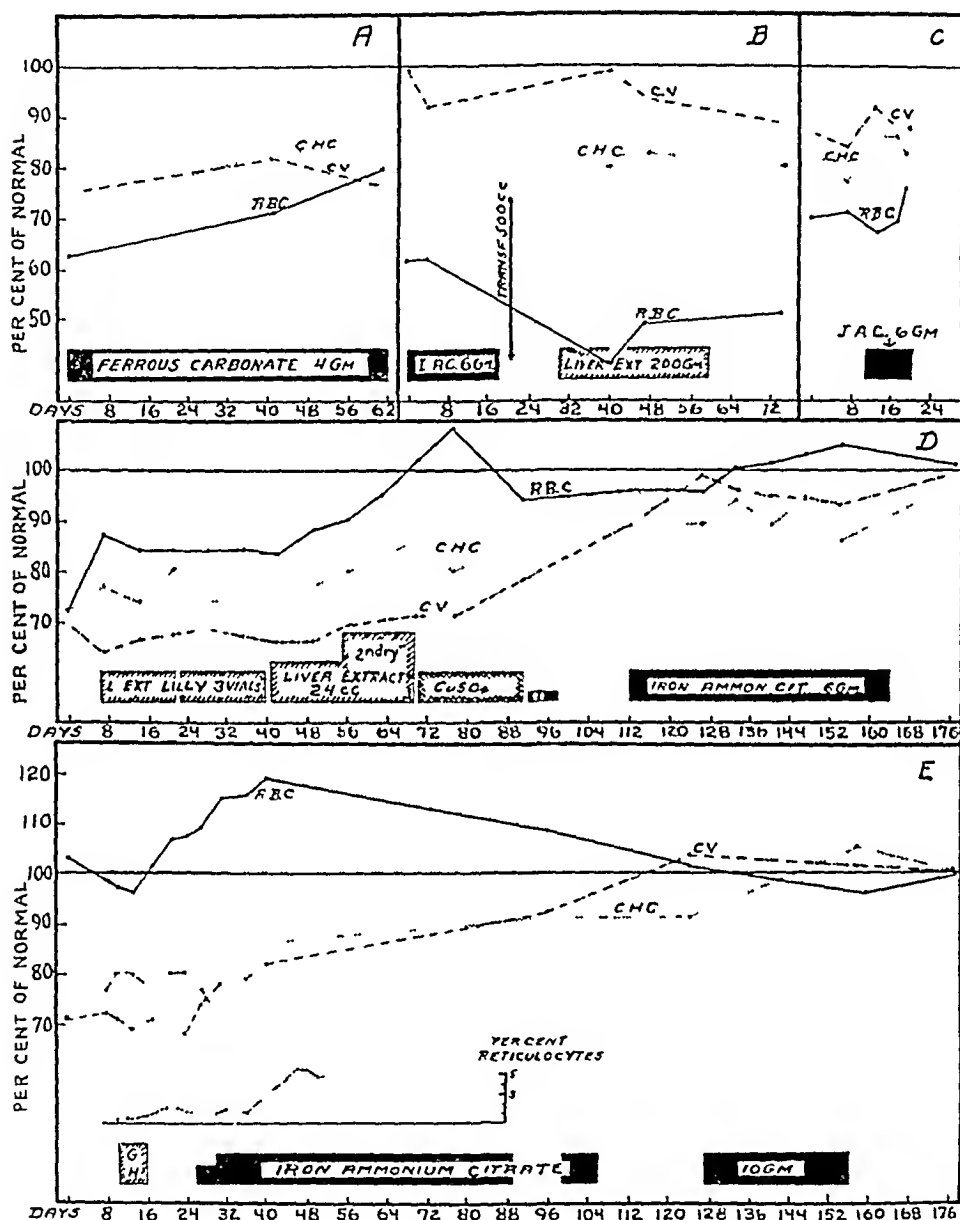


Chart 5—Hypochromic microcytic anemia. Variations in the mean corpuscular volume and in the mean corpuscular hemoglobin concentration in cases of chronic loss of blood due to carcinoma of the colon (A), carcinoma of the stomach (B and C) and hemorrhoids (D) and in a case of idiopathic hypochromic anemia (E)

5A) In the cases in which chronic loss of blood was the chief or sole disturbance, as in the cases of abortion, hemorrhoids, bleeding ulcer and hemorrhagic telangiectasia, good results were obtained even when the

cause of the loss of blood had not been treated. Under the influence of large doses of an iron preparation the erythrocyte count rapidly rose, frequently to temporary polycythemic values, the mean corpuscular volume rose, usually rapidly, to normal values, and the mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration increased until, under persistent treatment, they reached normal values (chart 5D). The administration of liver extracts effective in pernicious anemia, given orally or intramuscularly, and of desiccated hog stomach was ineffective in these cases, the action of copper was doubtful, and even the influence of liver extracts recommended for "secondary anemia"¹⁴ and of whole liver was, in comparison to that of large doses of an iron preparation, negligible.

2 Idiopathic Cases These cases (table 3) are of special interest. The majority of these, because of the presence of such symptoms as glossitis, paresthesia, koilonychia and achlorhydria as well as complaints characteristic of anemia in general, could be classed with the condition "idiopathic hypochromic anemia" described in detail elsewhere.¹³ Cases of the same type particularly associated with repeated pregnancies are grouped separately in table 3.

In addition there were 10 cases which could not be classified definitely. Two of these patients were suffering from hypertension. It is of interest that they were both women. Gastric analysis was done only on 1 of these, but in this patient achlorhydria was found. These cases may have represented the accidental association of two different conditions, namely, hypertension and "idiopathic hypochromic anemia."

In another of the 10 unclassified cases, hypochromic microcytic anemia was associated with chronic infectious arthritis. Interestingly enough, in this case treatment with an iron compound was followed by a good response, although in other cases of arthritis not associated with this type of anemia treatment was ineffective.

Another patient presented a clinical picture which was the nearest approach to true chlorosis that I have encountered. Five cases were not adequately studied and could not be classified. It is possible that, in several at least, undiscovered loss of blood had taken place.

The response to therapy in all these cases was the same (chart 5E) as in the cases of hypochromic microcytic anemia caused by chronic loss of blood and is discussed in detail elsewhere.¹⁵ The changes in the

¹⁴ Whipple, G. H., Robschert-Robbins, F. S., and Walden, G. B. Blood Regeneration in Severe Anemia. XXI. A Liver Extract Potent in Anemia Due to Hemorrhage, *Am. J. M. Sc.* **179**: 628 (May) 1930.

¹⁵ Beebe, R. T., and Wintrobe, M. M. Effect on Idiopathic Hypochromic Anemia of Beef Steak (Hamburger Steak) Digested with Normal Gastric Juice, *Arch. Int. Med.* **52**: 464 (Sept.) 1933. Wintrobe and Beebe.¹³

volume and hemoglobin content of the red corpuscles in these cases, in response to treatment with iron preparations, form an interesting contrast to the effects of liver therapy in pernicious anemia. Whereas, in the latter disease the mean corpuscular volume is closely correlated inversely with the erythrocyte count, in idiopathic hypochromic anemia the volume of the cells is correlated with the hemoglobin, and there is

TABLE 4—*Correlation Coefficients in Ninety-Four Cases of Pernicious Anemia*

Characters Correlated*	Determinations		Sex of Patients	Correlation Coefficient	Regression Coefficient
	Number	Kind			
R B C and C V	367	All	M	-0.7300 ± 0.0165	$C V = 145.9 - 11.9 \times R B C$
R B C and C V	289	R B C over 2,000,000	M	-0.8100 ± 0.0173	
R B C and C V	294	All	F	-0.6890 ± 0.0207	$C V = 136 - 10 \times R B C$
R B C and C V	253	R B C over 2,000,000	F	-0.7750 ± 0.0195	
Hb and C V	367	All	M	-0.4900 ± 0.0397	
Hb and C V	290	All	F	-0.5200 ± 0.0130	
Hb and C V	657	All	Both	-0.4950 ± 0.0291	
R B C and C C	749	All	Both	$+0.0997 \pm 0.0244$	
Hb and C C	753	All	Both	$+0.2922 \pm 0.0226$	
C V and C C	751	All	Both	-0.4270 ± 0.0202	

* R B C indicates erythrocyte count in millions per cubic millimeter, C V, mean corpuscular volume in cubic microns, Hb, hemoglobin in grams per hundred cubic centimeters, C C, mean corpuscular hemoglobin concentration (per cent)

TABLE 5—*Correlation Coefficients in Twenty-One Cases of Idiopathic Hypochromic Anemia*

Characters Correlated*	Number of		Sex of Patients	Correlation Coefficient	Regression Coefficient
	Determinations				
R B C and C V	339		F	$+0.1720 \pm 0.0356$	$C V = 2.6 Hb + 45$
Hb and C V	339		F	$+0.7520 \pm 0.0159$	
R B C and C C	331		F	$+0.4730 \pm 0.0286$	$C C = 1.04 Hb + 19.2$
Hb and C C	347		F	$+0.8990 \pm 0.0109$	
C V and C C	339		F	$+0.7450 \pm 0.0258$	

* Abbreviations are the same as for table 4

very little relation between the number of red corpuscles and the size of the cells (tables 4 and 5, chart 6). Again, in pernicious anemia the correlation between the mean corpuscular hemoglobin concentration and the number of erythrocytes or the amount of hemoglobin in the blood is very slight, but in idiopathic hypochromic anemia this correlation is high. Especially close is the relation between the hemoglobin and the mean corpuscular hemoglobin concentration. It is of interest that in both types of anemia the mean corpuscular volume and the mean corpuscular hemoglobin concentration are related, this correlation being

negative in pernicious anemia and positive in idiopathic hypochromic anemia

3 Hookworm Infestation The changes in the blood were the same as those described in the discussion of the cases of anemia resulting from chronic loss of blood. The response to treatment with iron preparations was likewise similar. This is of especial interest in view of the disagreement among investigators concerning the cause of hookworm anemia

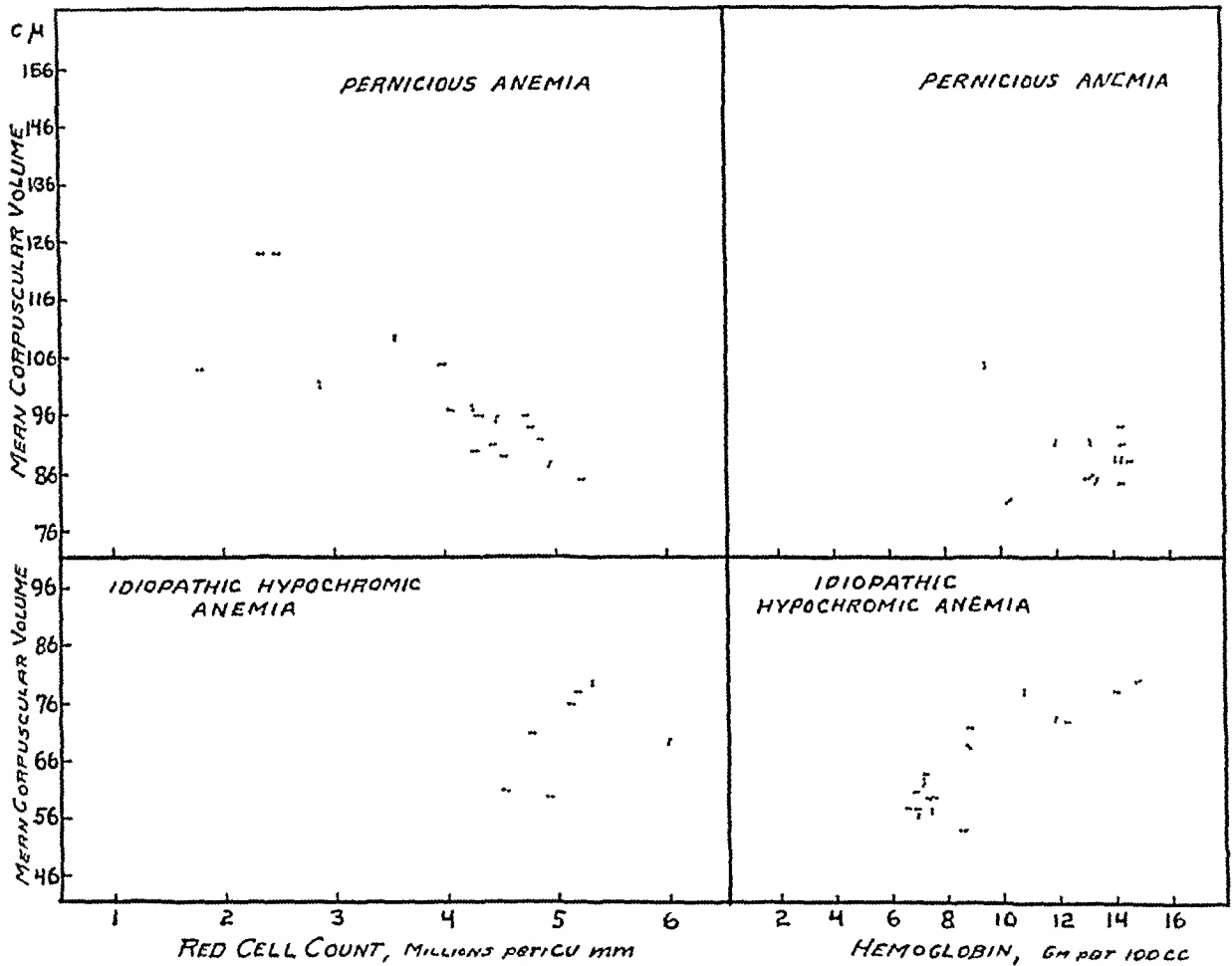


Chart 6—The relation of the mean corpuscular volume to the red cell count and to hemoglobin in pernicious anemia and in idiopathic hypochromic anemia. In pernicious anemia there is a high correlation between the mean corpuscular volume and the red cell count, in idiopathic hypochromic anemia between the mean corpuscular volume and the hemoglobin. The correlation coefficients are given in tables 4 and 5.

COMMENT

Analysis of the observations recorded suggests that differences in the mean volume and hemoglobin content of the red corpuscles are associated with fundamentally different pathologic disturbances in the formation of these corpuscles, and that the mean corpuscular volume and mean corpuscular hemoglobin concentration may be used as a clue

to the nature of this disturbance as well as to the type of therapy which may be expected to be effective

The macrocytic anemias recorded in table 3 seem to fall into two groups. Pernicious anemia and the other conditions associated with glossitis and diarrhea, as well as the macrocytic anemias associated with pregnancy, form one group which is distinguished by a striking increase in the volume and hemoglobin content of the erythrocytes and a ready response to liver therapy. These probably form, with celiac disease or idiopathic steatorrhea¹⁶ and the tropical anemia of Wills,¹⁷ as well as with the rare instances of carcinoma of the stomach which are associated with macrocytic anemia, a group of anemias which depend for their development on the absence of what may be called the X hematopoietic principle. This principle is presumably formed by the combination of an unknown "extrinsic" substance and a substance secreted by the gastric juice.¹⁸ The lack of the extrinsic factor in the diet (tropical anemia¹⁷), defective gastric secretion of the intrinsic factor (pernicious anemia, rare instances of carcinoma of the stomach and perhaps also "pernicious anemia of pregnancy"¹⁹) or defective absorption of the combined "intrinsic" and "extrinsic" factors (sprue [?],²⁰ celiac disease [?]¹⁶) may lead to the development of macrocytic anemia by causing a break in the metabolic chain.

The significance of the other instances of macrocytic anemia found in table 3 is less clear. It has been suggested that the development of macrocytic anemia in certain cases of hepatic disorder may be due to faulty storage of the X principle.¹² It is doubtful whether the other two groups of cases associated with macrocytic anemia which are shown in table 3 (conditions associated with disturbance of the bone marrow and several cases of acute posthemorrhagic anemia) should be classed with the cases of "true" macrocytic anemia. The macrocytosis in these cases was not as great as that which occurs in pernicious anemia, and in the cases in which liver therapy was attempted such treatment certainly was not followed by the spectacular response which occurs in the "true" macrocytic anemias. It is of interest that these same two

16 Bennett, T. I., Hunter, D., and Vaughan, J. M. Idiopathic Steatorrhea (Gee's Disease). A Nutritional Disturbance Associated with Tetany, Osteomalacia and Anaemia, *Quart J Med* **1**:603 (Oct) 1932.

17 Wills, L. Treatment of "Pernicious Anemia of Pregnancy" and "Tropical Anemia," *Brit M J* **1** 1059, 1931.

18 Strauss, M. B., and Castle, W. B. The Nature of the Extrinsic Factor of the Deficiency State in Pernicious Anemia and in Related Macrocytic Anemias, *New England J Med* **207** 55 (July 14) 1932.

19 Strauss, M. B., and Castle, W. B. Studies of Anemia in Pregnancy, *Am J M Sc* **185** 539 (April) 1933.

20 Castle, W. B., and Rhoads, C. P. Aetiology and Treatment of Sprue in Porto Rico, *Lancet* **1**:1198 (June 4) 1932.

groups of cases are also represented, actually in greater numbers, in the normocytic group of anemias. On the whole the cases associated with disturbance of the bone marrow and with acute loss of blood in which macrocytic anemia was found were more severe and revealed more evidence of stimulation of the bone marrow than the cases of the same nature in which no significant alterations in the mean volume and hemoglobin content of the red cells occurred. In view of the observation²¹ that in pernicious anemia reticulocytosis is associated with a temporary increase of macrocytosis and that the appearance of large numbers of reticulocytes significantly increases the mean size of the circulating red corpuscles in other types of anemia, it seems probable that the cases of acute loss of blood and of anemia associated with disturbance of the bone marrow in which macrocytic anemia was found were fundamentally the same as those in which normocytic anemia was observed, differing only in that the anemia had become so marked and the stimulation of bone marrow so intense that some increase above the normal in the mean volume and hemoglobin content of the red corpuscles took place.

Judging by the nature of the conditions under which normocytic anemia was found, one might consider this type of anemia as developing through (1) sudden loss of blood, (2) acute destruction of blood (malaria) and (3) lack of blood formation (aplastic anemia). In the first two instances no change in the red corpuscles found in the circulation would be expected to take place until stimulation of the bone marrow occurred. It may be postulated that when this stimulation is only moderate, no change is observed in the mean volume and hemoglobin content of the red cells. When it is marked some macrocytosis may develop.

That the erythrocytes which still remain in the circulation in aplastic anemia would be normal in size and hemoglobin content is to be expected, for the bone marrow in such cases is unable to form new cells. It is of interest that in the case of aplastic anemia in which recovery eventually took place the period of improvement was marked, as in the cases of acute posthemorrhagic anemia in which stimulation of the bone marrow was great, by the development of moderate macrocytosis. In the cases of anemia associated with disturbance of the bone marrow, normocytic anemia may likewise be expected, since the anemia in such cases may be due in a large measure to crowding out of otherwise normally functioning erythrogenic tissue by leukemic or other

21 Wintrobe, M. M. Relation of Variations in Mean Corpuscular Volume to Number of Reticulocytes in Pernicious Anemia. The Significance of Increased Bone Marrow Activity in Determining the Mean Size of Red Corpuscles, *J. Clin. Investigation* **13** 669 (July) 1934.

infiltrative growths. There is no deficiency in the X principle, as in the "true" macrocytic anemias, or in iron, as in the hypochromic microcytic anemias.

The remaining cases in the normocytic group (those associated with inflammatory and noninflammatory diseases of various kinds, nephritis and pregnancy) are very similar to cases of simple microcytic anemia, the chief difference being that in the latter some microcytosis, usually only moderate in degree, developed. The anemia in all these cases, which form the greater proportion of the so-called "secondary anemias," is probably the result of imperfect formation of red cells brought about by the toxic influence of disease in general. One may imagine such an influence to lead to physiologic hypoplasia of the bone marrow with the consequent development of normocytic anemia or to cause imperfect erythropoiesis with the formation of red corpuscles somewhat smaller than normal and yet moderately well filled with hemoglobin. Therapy in this type of anemia is of little value without the removal of the cause,²² and its recognition is important chiefly for this reason.

The hypochromic microcytic anemias, like the "true" macrocytic anemias, form a clearly defined group which it is important to distinguish. The essential morphologic characteristic of this group is a definite and well marked decrease below normal in the mean corpuscular hemoglobin concentration. This decrease is conditioned by a deficiency in hemoglobin which results from long continued loss of blood or, in some cases, probably by a defective absorption of hemoglobin—building material from the diet (idiopathic hypochromic anemia²³). Defective diet may possibly lead to the same result. The therapeutic effect of iron in this type of anemia is as consistent and spectacular as is liver therapy in pernicious anemia and seems often to occur in the presence of the cause of the anemia. Thus chronic posthemorrhagic anemia may be temporarily relieved by the administration of large doses of iron even though the source of the loss of blood remains, and idiopathic hypochromic anemia is readily treated in the same way although cessation of treatment is often followed by relapse.

The relation of morphologic differences in the red corpuscles to different types of disorder in the hematopoietic apparatus which has been outlined is summarized in the classification of anemia presented in table 6.

The value of the classification proposed has necessarily been limited heretofore to the test of my own experience, and it is therefore impos-

22 Wright, G. P., and Arthur, B. The Influence of Liver Extract Effective in Pernicious Anemia upon the Diameter of Erythrocytes in Experimental Anemias, *J. Path. & Bact.* **33** 1017 (Oct.) 1930. Murphy, W. P., and Fitzhugh, G. Red Blood Cell Size in Anemia, *Arch. Int. Med.* **46** 440 (Sept.) 1930.

TABLE 6—*Classification of Anemias*

Type of Anemia	Corpuscular Volume, Cubic microns	Hemo- globin Concen- tration, per Cent	Cause	Clinical Syndrome	Treatment
I Macrocytic	>94*	>30†	A Deficiency of Castle's anti-anemic principle	(1) Pernicious anemia (2) "Pernicious anemia" of pregnancy (3) In rare cases of (a) carcinoma of the stomach and other diseases of the stomach and intestines (b) total gastrectomy (c) pellagra (4) Tropical anemia of Wills (5) Sprue (6) Macrocytic anemia of echin disease (7) Macrocytic anemia of liver disease (?)	Liver or liver extract, or "extrinsic factor" if this alone is deficient
			B Intense activity of bone marrow	Conditions usually associated with normocytic anemia (section II)	Transfusions and treatment of cause
II Normocytic	80 to 94	>30	A Sudden loss of blood	Acute posthemorrhagic anemia, e g, hemolytic anemia caused by malaria	Transfusions
			B Acute destruction of blood		Treatment of cause
			C Lack of formation of blood	(1) Aplastic anemia (idiopathic and secondary) (2) Conditions which decrease amount of functioning bone marrow, e g, leukemia, neoplasms (3) Chronic inflammatory and noninflammatory diseases	Attempts to stimulate formation of blood
			D Hydremia (?)	"Physiologic" anemia of pregnancy	
III Simple microcytic	<80	>30	"Imperfect" formation of blood	Subacute and chronic inflammatory diseases and chronic noninflammatory conditions	Transfusions and treatment of cause
IV Hypochromic microcytic	<80	<30	Deficiency of iron, through	{ Chronic posthemorrhagic anemia	Iron in large doses
			A Loss of blood	{ Hookworm anemia	Correction of cause
			B Defective diet	{ Diet deficient in foods containing iron Chlorosis (?)	
			C Defective absorption	{ Idiopathic hypochromic anemia following total gastrectomy (some cases) Sprue (some cases) Idiopathic steatorrhea (some cases) Hypochromic anemia of pregnancy	
			D Excessive demands for iron (repeated pregnancies)	{	

* The sign > indicates "greater than"

† The sign < indicates "less than"

sible to predict whether all cases will come within the scope of the subdivisions proposed. Furthermore its usefulness is also limited by the fact that when the degree of anemia is only slight, the alterations in the size and hemoglobin content of the red corpuscles may not be pronounced, thereby making it difficult to classify the anemia on these grounds. Finally, cases of anemia caused by more than one factor are encountered from time to time, and such cases present much difficulty in classification.

It is obviously wise not to attempt classification of the anemia on the basis of a single examination of the blood, except in the more obvious cases. Moreover, it must be emphasized that unless the technic described is painstakingly followed and great care taken to secure accuracy, this method of classification will be not only valueless, but actually misleading.

The fundamentally important and practical merit of the classification proposed is that it makes possible the ready differentiation of pernicious and similar types of anemia which are effectively treated by liver therapy from those which are effectively treated with iron preparations and permits the separation of these from the types of anemia in which neither liver nor iron, nor both combined, is of any value.

SUMMARY AND CONCLUSIONS

Observations on the volume and hemoglobin content of the erythrocytes of more than 1,000 healthy and anemic persons are recorded and discussed under the heads of accuracy of the methods employed, normal values, physiologic variations and variations in disease.

The anemias may, on the basis of differences in the mean volume and hemoglobin content of the red corpuscles, be subdivided into four groups. Each of these groups appears to correspond to a fundamentally different type of disturbance in the hematopoietic apparatus.

Consequently the method of classification proposed is useful as an aid to diagnosis. It facilitates also the separation of conditions in which liver therapy may be expected to be of value from those in which treatment with iron preparations is successful, and distinguishes these two types of anemia from those in which neither method of treatment can be expected to succeed.

J. Walter Landsberg gave technical assistance.

PERNICIOUS ANEMIA

PARENTERAL TREATMENT WITH EXTRACTS PREPARED FROM DIGESTED
EQUINE LIVER AND FROM SELF-DIGESTED STOMACH

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AND

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H LEGERE

CHICAGO

The presence of an antianemic factor in hog stomach and its therapeutic effectiveness in the treatment of pernicious anemia were discovered by Sharp¹ and Sturgis and Isaacs². The active principle present in stomach tissue was found to be thermolabile, and could not be extracted by the method of Cohn, used in preparing liver extracts. They further found that no therapeutic response was obtained when either the muscularis or the mucosa of the stomach was fed separately. It was necessary to administer both in order to obtain the active principle. This suggested that the interaction of an enzyme on protein, present in the whole stomach tissue, occurred after the organ was removed. However, the observations of Castle,³ that by the action of normal gastric juice on muscle meat the active factor was formed, and of Morris,⁴ that normal gastric juice contains this principle, indicated that the substance was being formed in some way by normal gastric activity. In a previous report we⁵ demonstrated that the activating principle stored in the liver was completely depleted during a relapse in patients with pernicious anemia.

From the Laboratories of the Chappel Foundation for Organotherapeutic Research, Rockford, Ill, and Cook County Hospital, Chicago

1 Sharp, E A. An Antianemic Factor in Desiccated Stomach, J A M A 93 749 (Sept 7) 1929

2 Sturgis, C C, and Isaacs, R. Desiccated Stomach in the Treatment of Pernicious Anemia, J A M A 93 747 (Sept 7) 1929

3 Castle, W B. Effect of Administration to Patients with Pernicious Anemia of Contents of Normal Human Stomach Recovered After Injection of Beef Muscle, Am J M Sc 178 748, 1929

4 Morris, R S, Schiff, L, Burger, G, and Sherman, J E. A Specific Hematopoietic Hormone in Normal Gastric Juice, J A M A 98 1080 (March 26) 1932, Hematopoietic Response in Pernicious Anemia Following Intramuscular Injection of Gastric Juice, Am J M Sc 184 778, 1932

5 Richter, O, Ivy, A C, and Kim, M S. Action of Human "Pernicious Anemia Liver Extract," Proc Soc Exper Biol & Med 29 1093, 1934

The question as to the nature of this substance became still more complex when it was shown by Walden and Clowes⁶ and by Fouts and Zerfas⁷ that the product of the interaction of liver or liver extract and hog gastric tissue substantially increased the antianemic factor and its therapeutic potency. Reimann⁸ also reported a marked increase in the potency of liver digested in normal gastric juice following stimulation with histamine. On the other hand, Barnett and Thebaut⁹ found that liver or liver extract digested in normal gastric juice was no more effective therapeutically than the equivalent amount of liver or liver extract when given alone. Similar experiments by Helmer, Fouts and Zerfas¹⁰ demonstrated that subminimal amounts of liver extract, when incubated with normal gastric juice and fed daily to patients with pernicious anemia, produced maximal reticulocyte responses.

On considering these facts, the question arises as to whether the increase in potency was due to the additive effects of liver and stomach, to a more complete extraction of liver pulp during the process of digestion or to an actual multiplication of the active substances. The work of Herron and McEllroy¹¹ further excluded the possibility of an additive action of stomach and liver, since they proved that autolyzed liver was more potent than fresh liver when given by mouth or parenterally in pernicious anemia. The experience with oral application makes it improbable that the increased potency of their preparation was due primarily to a more effective extraction of the active principle. It is possible that the autolysis splits off the same products from liver as normal gastric juice, but that the usually anacid gastric juice of patients with pernicious anemia is unable to bring this about.

We have previously reported¹² that complete hematologic remissions can be produced in patients with pernicious anemia following injections

6 Walden, G. B., and Clowes, G. H. A. Pernicious Anemia. Method Whereby Therapeutic Efficacy of Liver and Liver Fractions May Be Substantially Increased, *Proc Soc Exper Biol & Med* **29** 873, 1932.

7 Fouts, P. J., and Zerfas, L. G. Liver Gastric Tissue Preparations in the Treatment of Pernicious Anemia, *J A M A* **101** 188 (July 5) 1933.

8 Reimann, F. *Med Klin* **27** 880, 1931.

9 Barnett, C. W., and Thebaut, W. M. Treatment of Pernicious Anemia with Digested Liver, *J A M A* **99** 556 (Aug 13) 1932.

10 Helmer, O. M., Fouts, P. M., and Zerfas, L. G. Increased Potency of Liver Extract by Incubation with Human Gastric Juice, *Proc Soc Exper Biol & Med* **30** 775, 1933.

11 Herron, W. F., and McEllroy, W. S. The Use of Autolyzed Liver in the Treatment of Pernicious Anemia, *J A M A* **100** 1084 (April 8) 1933.

12 Meyer, A. E., Richter, O., and Ivy, A. C. Pernicious Anemia. Treatment with Equine Liver Extract. Injectible Either Subcutaneously or Intravenously, *Arch Int Med* **50** 538 (Oct) 1932, Further Observations in the Treatment of Pernicious Anemia with Parenteral Horse Liver Extract, *Ann Int Med* **7** 353, 1933.

of purified equine liver extract. In a series of fifty-nine patients studied it was found that an average of from one to two ampules (one ampule containing 2.5 cc or 25 Gm of equine liver) injected subcutaneously each day was necessary to produce a maximal reticulocyte response. The injections of two ampules a day were usually required in patients with complications.

The purpose of this study was to determine, if possible, whether by treating equine liver with stomach tissue one could obtain a predigested liver extract suitable for injection and with increased potency as compared with standard equine liver extract. Clinical tests were also made with an extract suitable for injection prepared from the mucosa of horse stomach. The method employed in preparing this extract was similar to that employed by Cohn in preparing liver extract. If such a preparation should be proved potent, the conception that the principles present in liver and stomach are identical, at least as to their chemical nature, would receive considerable support. Gebhardt and Cario¹³ obtained reticulocyte responses, but without any apparent increase in hemoglobin and erythrocytes, by the injection of an extract prepared from digested beef. Donati and his associates¹⁴ reported complete blood remissions in two patients treated with a diluted extract representing 0.3 Gm of stomach per cubic centimeter, but the method of preparation was not given.

PREPARATION OF EXTRACTS

Predigested Liver Extract—Twenty-five pounds (11.34 Kg) of horse liver and 5 pounds (2.27 Kg) of stomach mucosa from the horse were ground finely and mixed with 9 liters of water, and hydrochloric acid was added to bring the pH to 4.7. This was allowed to stand from three to four hours at a temperature of 40 C, then heated to 82 C to precipitate proteins and pressed out, and the liquid was filtered. The pH of the resulting liquid was 6. The water-soluble extract was then fractionated with alcohol, approximately as in Cohn's¹⁵ method for preparing fraction G. The various steps of purification connected with the elimination of mostly heavy precipitates carry a certain loss of activity, and extraction is furthermore incomplete because some of the liquid remains in the residue. On account of this difficulty the residue in every step was weighed, and the content of liquid determined. Taking into account the volume of liquid which was obtained from

13 Gebhardt, H., and Cario, R. Die Wirkung von Magensaft und einigen Verdauungsproducten auf Reticulocyten Zahl und Blutregeneration, *Deutsche med Wchnschr* **58** 726, 1932.

14 Donati, A., Manginelli, L., and Tramonti, E. Parenteral Treatment with Stomach Extract in Pernicious Anemia. *Minerva med* **2** 6 (July 7) 1931. *Rev sud-am endocrinol* **15** 598, 1932.

15 Cohn, E. J., Minot, G. R., Fulton, J. F., Ulrichs, H. F., Sargent, F. C., Weare, J. H., and Murphy, W. P. *J Biol Chem* **74** LXIX, 1927. Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. I. The Nature of the Material in Liver Effective in Pernicious Anemia. *J Biol Chem* **77** 325, 1928.

the residue, the relative yield in each step could be calculated, and later the total yield of preserved activity was found by the multiplication of these values. In this way it was possible to determine how much raw material was represented in the final fraction.

The final precipitate, representing 46 per cent of the liver employed, or 5.22 Kg., was then dissolved in a convenient amount of water, and a phosphate buffer was added in order to make the solution isotonic and to adjust the pH of the finished product to 6.7.

On account of the high concentration of split protein products, the determination of pH by both the indicator and the quinhydrone method is unreliable. The apparent value of 6.7 was found to give a rather painless injectible material. The potency of the extract was then standardized so that 1 cc. of the extract represented 10 Gm. of liver and 2 Gm. of stomach mucosa, to which 0.4 per cent of cresol was added as a preservative. The solution was then heated for a short time at 100 C., filtered and sealed in ampules. The dry residue in this predigested extract was 18.8 per cent as compared with 5 per cent in the standard undigested equine liver extract prepared by the same method.

Injectible Extract from Stomach Mucosa—Twenty pounds (9.07 Kg.) of horse stomach mucosa was ground and mixed with 6 liters of water and sufficient hydrochloric acid to make a pH of 4.7. This mixture was then heated to between 38 and 40 C. for four hours under constant stirring. The temperature was then raised to 82 C., after which the pH had changed to 5.5. A solution of sodium hydroxide was added until the pH was brought up to 6.5. The residue was pressed out and discarded. The filtrate was very thick, and represented 79 per cent of the raw material. Fractionation was then carried out by the method used in the preparation of the predigested liver extract. The final precipitate corresponded to 6.6 Kg., which represented about 72.8 per cent of the original stomach tissue. The precipitate was dissolved in water to a total volume of 600 cc., so that 1 cc. represented 11 Gm. of stomach mucosa. A phosphate buffer was added, and the pH was adjusted to 6.9 by the bromthymol blue method, which gave a reading of 7.05 by the quinhydrone electrode method. The final residue in this extract was 13 per cent, to which 0.4 per cent of cresol was added as a preservative. The solution was then heated for a short time at 100 C., filtered and sealed in ampules.

Preliminary animal and laboratory tests were made to establish the safety of this material for parenteral administration. Its sterility was tested by culture. The absence of anaphylactic effects was shown on guinea-pigs. Irritating qualities were found to be absent by subcutaneous injections into rabbits. Intravenous injections into rabbits produced no visible reaction. The vasodepressor action, measured by the assay of blood pressure on dogs, showed no significant histamine-like fall in blood pressure.

CLINICAL AND EXPERIMENTAL OBSERVATIONS

Eight patients with pernicious anemia were studied. Daily reticulocyte counts were taken during the expected period of maximal response. Complete examinations of the blood were made at five day intervals throughout the entire period of treatment.

We had previously determined that daily injections of one ampule (2.5 cc. or 25 Gm. of equine liver) of standard liver extract were necessary to produce a maximal reticulocyte response and a prompt hematologic remission in patients with pernicious anemia without com-

plications Therefore, in order to ascertain the relative potency of predigested liver extract to standard equine liver extracts, a comparative study was made on patients who were given subminimal doses of predigested liver extract Three patients (cases 1, 2 and 3) were given injections of predigested liver extract at two day intervals A maximal reticulocyte response of 32.2 per cent was obtained in case 1 on the eighth day, of 25.2 per cent in case 2 on the eighth day and of 31.6 per cent in case 3 on the seventh day In addition,

TABLE 1—*The Response of Six Patients with Pernicious Anemia to Subcutaneous Injections of Predigested Equine Liver Extract*^{*}

Case, Patient	Age	Relapse	Treat- ment, Days	Maximal Reticu- loocyte Count, per Cent	Hemoglobin % (Sahlb)		Red Blood Cells, Millions		Total No of Injec- tions, 2.5 Cc	Comment
					Before	After	Before	After		
1† L D	51	1	44	32.2	35	83	1.39	4.45	22	Involvement of posterior columns improved at the end of treatment
2† J Mc	64	2	39	25.2	29	83	1.11	4.15	19	Marked mental improvement
3† E J	72	3	63	31.6	36	81	1.26	4.11	32	In stupor when admitted, with extreme emaciation and spastic paralysis
4† M O	48	1	40	26.4	19	70	0.69	3.55	40	In stupor when admitted, left before end of treatment
5† P M	59	2	73	27.6	22	80	0.91	4.48	73	Moribund when admitted, incontinent, intermittent attacks of severe diarrhea throughout treatment
6§ E K	47	1	16	57.2	16	60	0.64	3.02	19	Still on treatment

* The standard dosage was one ampule of predigested equine liver extract (2.5 cc), which represented 25 Gm. of liver and 5 Gm. of stomach mucosa

† Received one ampule every two days

‡ Received one ampule daily

§ Received two ampules daily during the period of maximal reticulocyte response and then one daily

prompt remissions and excellent clinical recoveries were obtained It was apparent, at least in these three patients, that the effect from predigested liver extract given every second day was identical to that produced in patients receiving daily injections of standard equine liver extract

Since it was frequently necessary to give injections of two ampules (50 Gm. of equine liver) a day of standard liver extract to patients with complications, comparative studies were made of the reactions of two patients having intractable diarrhea and advanced degeneration of the spinal cord to daily injections of predigested liver extract Case 4 (table 1) showed a reticulocyte response of 26.4 per cent on the sixth

day and case 5 (table 1) a reticulocyte response of 27.6 per cent on the seventh day. Satisfactory gains in the hemoglobin content and erythrocyte count were also obtained during the period of treatment. It is difficult to draw any definite conclusions from the observation of these two patients as to the relative potency of predigested equine liver extract, as it is known that the liver requirement varies in individual patients with pernicious anemia, particularly in those with complications.

One patient (case 6, table 1), a white man, 47 years of age, entered the hospital with a complete relapse and in a semistuporous condition. On entrance the hemoglobin determination was 16 per cent (Sahli) and the erythrocyte count 640,000. Because of the patient's poor condition two ampules of predigested liver extract were administered daily. A reticulocyte response of 57.2 per cent was obtained on the sixth day of therapy (table 2). At the end of seventeen days of treatment, the

TABLE 2—*Reticulocyte Response to Injections of Predigested Liver Extract in Case 6*

Days of Treatment	Hemoglobin, % (Sahli)	Red Blood Cells, Millions	Reticulocytes, per Cent
1	16	0.64	1.0
2			0.2
3			4.4
4			7.6
5			25.6
6	27	1.07	57.2
7			7.6
8			4.2
9			2.2
12	53	2.85	0
17	60	3.02	0

hemoglobin content was 60 per cent (Sahli) and the erythrocyte count 3,020,000. The therapeutic response produced in this patient surpassed any yet obtained by a similar amount of standard equine liver extract.

The injectible extract prepared from horse stomach mucosa was administered to two patients with uncomplicated pernicious anemia, both entering the hospital after their second relapse. Patient L. B. (chart 1) received one ampule a day of stomach mucosa extract (2.5 cc = 5 Gm.), and although a reticulocyte response of 14 per cent was obtained on the fifth day, there was no increase in the hemoglobin or erythrocyte count during seventeen days of treatment. One ampule of standard liver extract (2.5 cc = 25 Gm. of equine liver) was then injected daily, and a second reticulocyte response of 8.6 per cent occurred, but still there was no increase in the erythrocyte count and only a slight elevation in the hemoglobin content at the end of seven days. Predigested liver extract was then substituted, one ampule (2.5 cc = 25 Gm. of liver and 5 Gm. of stomach mucosa) being given daily. A third, but only moderate reticulocyte response (3.6 per cent) was obtained on the sev-

enth day, but there was remarkable increase in the hemoglobin content (from 25 to 50 per cent, Sahli) and in red blood cells (from 1,230,000 to 2,410,000) at the end of fifteen days of treatment

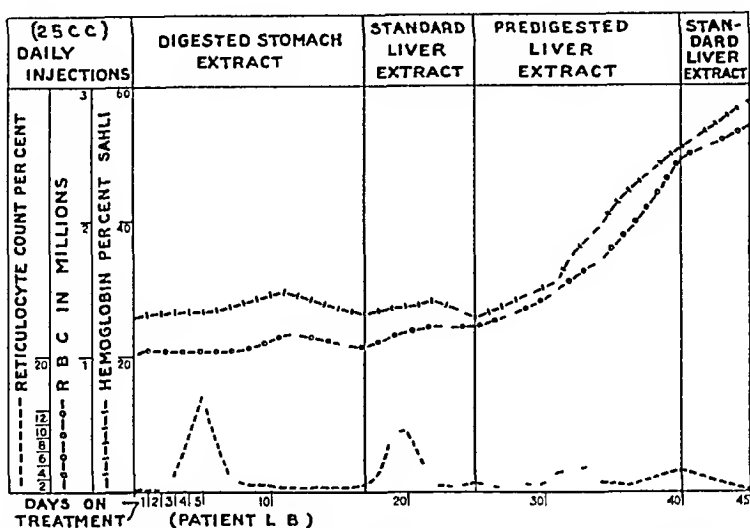


Chart 1—Blood changes in a case of pernicious anemia during periods of daily injections of digested stomach extract, standard liver extract and predigested liver extract

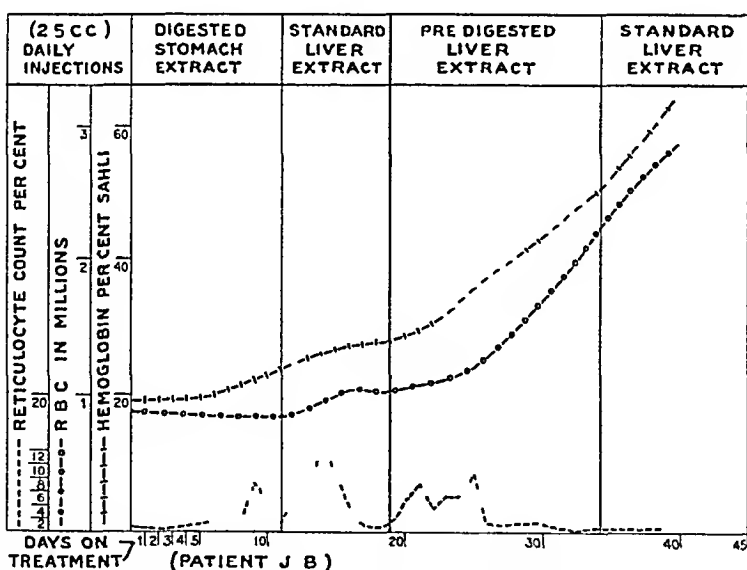


Chart 2—Blood changes in a case of pernicious anemia during periods of daily injections of digested stomach extract, standard liver extract and predigested liver extract

A similar experiment was carried out on patient J B (chart 2). Although the maximal reticulocyte response of 13 per cent was obtained on the third day of treatment with standard liver extract, the greatest

increase in the hemoglobin content and erythrocyte count was noted while the patient received daily injections of predigested liver extract

Because of the varying responses of patients with pernicious anemia when treated with preparations containing the antianemic factor, the problem of determining accurately the potency of the active principle presents great difficulty. Therefore, we feel that only comparative studies of these extracts can be presented in this paper.

CONCLUSIONS

1 An injectible extract with increased potency was prepared from the interaction of horse liver and horse stomach mucosa (2.5 cc = 25 Gm of horse liver and 5 Gm of horse stomach mucosa)

2 An extract prepared from horse stomach mucosa (2.5 cc = 27.5 Gm of horse stomach mucosa), when injected into patients with pernicious anemia, produced a moderate reticulocytosis, but no increase in the hemoglobin content and erythrocyte count

CURABILITY OF HAY FEVER AFTER PRESEASONAL POLLEN TREATMENT

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In a previous article I reported a series of 100 patients apparently cured after preseasonal treatment for pollen hay fever. They were treated for varying periods during the interval from 1919 to 1925, inclusive, and were followed up for two or more years after the cessation of treatment. The present article reports a second series of 90 patients who were treated preseasonally for various periods during the interval from 1923 to 1930 and who have been followed up for three or more years since the cessation of treatment. The records of these 90 are presented in tables 1 and 2. Table 3 shows the inadvisability of stopping treatment too soon. Finally, in table 4 are presented statistics computed from all the patients treated preseasonally during the interval from 1919 to 1930, including those reported in the former article, as well as those of this series.

METHOD AND MATERIALS OF TREATMENT

As a rule the patients were treated at weekly intervals, and the few who were not were treated at five day intervals. No shorter intervals between treatments were used. In most of the cases the treatment was entirely preseasonal, usually beginning about fifteen weeks previous to the expected onset of symptoms. In a few instances when patients presented themselves two or three weeks late, one or, rarely, two inoculations were given after the onset of symptoms, thus no patients in this series were given what is termed during-the-season treatment. In all instances careful cutaneous tests were performed with the various dilutions of the causative pollens in order to determine with what dilution or strength of pollen extract treatment should be begun. This was most important since without this test some patients would be given too strong treatment at the start, resulting in reactions, and others would be given unnecessarily weak treatment. Without the graduation tests there is no definite plan of treatment. Tests with the graduated pollen dilutions are a guide in determining the successive increases in dosage. It is evident that the results from commercial pollen extracts, which are dispensed with the same schedule of treatment for every one, are not comparable to the results obtained by those who make careful tests or to the results presented in this paper.

Pollens Used for Treatment—In New England patients with hay fever are more fortunate than those in other parts of the country because the hay fever-producing flora is limited. The variable changes in the weather and frequent rainy days in the spring alleviate the sufferings of those subject to tree hay fever to such an extent that treatment seems unnecessary. In the late spring, during May

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and early June, depending on the seasonal weather, only in rare cases does the pollen of June grass cause sufficient hay fever to justify treatment. In a few other cases the pollen of June grass causes symptoms for three weeks, but treatment is not essential. Lawn grass and orchard grass cause irritation during June, but the former is short, so that close contact can be avoided fairly well, and the latter is prevalent only in small and scarce plots. The two grasses which cause practically all the hay fever in New England are red top and timothy, both of which may pollinate from early June to late July. In my experience sufficient treatment with an extract of the pollen of timothy protects against exposure to red top pollen. Therefore, all the patients with hay fever in early summer presented here and in the former article¹ were treated with an extract of timothy pollen alone, patients otherwise treated are not included.

In the late summer or autumn the New England plants producing hay fever are even more limited, since the dwarf or small ragweed is responsible for practically all the hay fever with the exception of some giant ragweed in Connecticut. Therefore, in this and the former study all the patients were treated with an extract of small ragweed pollen. The results presented are not comparable to those obtained with commercial pollen extract since the commercial extracts are mixtures and since some of the ingredients are not needed in this locality. Neither are the results comparable with those obtained in other parts of the country because there, owing to the variety of causative pollens, mixtures of pollens must of necessity be used.

Preparation of Pollen Extracts—One gram of the dried pure pollen is extracted for twenty-four hours in 88 cc of physiologic solution of sodium chloride, after which 12 cc of absolute alcohol is added and extraction continues for another twenty-four hours. With each extraction the mixture is shaken for an hour, the remainder of the extraction is carried on in an icebox. To the clear extract phenol is added to make the solution 0.25 per cent. This stock solution is probably a saturated solution since a repetition of this procedure on the same pollen will produce an extract strong enough to give positive reactions in concentrated dilutions. It is a 1:100 dilution, and from it are made other progressively weaker dilutions up to 1:160,000. Each patient is tested and treated according to the tests with the various dilutions. The first treatment is given with the strongest dilution that fails to give a cutaneous reaction, and succeeding treatments are gradually increased through the progressively stronger dilutions, with the aim to give at the end of treatment three or four doses of the 1:500 dilution. Any dose that causes local or general reaction is repeated on the scheduled date before the succeeding increase is given.² Commercial houses in general and most internists use pollen extracts that are made in different ways, therefore their results may not be comparable.

Index of Cure—In the former article on apparent cures it was concluded that when the cutaneous reaction to the causative pollen became negative it was safe to stop treatment. This conclusion has been proved correct, since no relapses have occurred in such cases up to the present time. Another conclusion was that when the pollen reaction does not become negative it is desirable that the patient show considerable decrease in sensitivity and have at least one and preferably two seasons of complete freedom from hay fever while under treatment before treatment

1 Walker, I. Chandler. One Hundred Cases of Apparently Cured Pollen Hay Fever, *J. A. M. A.* 90:750 (March 10) 1928.

2 Walker, I. C. Frequent Causes and the Treatment of Seasonal Hay-Fever, *Arch. Int. Med.* 28:71 (July) 1921.

is discontinued. This has proved to be the next best guide and the only other index as to whether the patient may remain free from symptoms for years after the omission of treatment or may be apparently cured. Only 1 patient in the former series has had a relapse. Therefore these two conclusions have been the guides to indicate when an apparent cure was probable with the series presented in tables 1 and 2.

RESULTS RECORDED IN TABLE 1

By comparing the columns of table 1 representing the sensitivity before any treatment and the sensitivity the last year of treatment it is evident what change took place in the sensitivity of the patient following the various seasons of treatment. The cutaneous tests were made preceding the course of treatment in every case and they were not made at the end of any individual course of treatment. This explanation is opportune since it is known that the sensitivity is usually greatly reduced at the end of any course of treatment, but that it may not be permanent and that it usually increases from this point during the period of months that elapses between courses of treatment. The final tests recorded were made just preceding the final year's treatment and therefore give a permanent rather than a temporary estimate of sensitivity, in fact, since the final course of treatment followed these tests the patients are probably even less sensitive than these data show. The series of columns headed "Result Without Treatment" represent the years in which no treatment was given and the amount of hay fever that the patient experienced during these respective years.

Incidence, Age of Onset and Duration—In this group were 27 men and 28 women. The age of onset of hay fever ranged from 1 to 57 years, 6 of the 55 began to have hay fever after reaching the age of 40 and 11 began to have symptoms before the age of 10. The duration of hay fever before treatment varied from one to thirty years, 6 had had symptoms for twenty or more years. None of these factors seemed to have much bearing on the curability or the duration of treatment.

Sensitivity—Of the 55 patients, 21 were treated with the pollen extract of timothy grass and 34 with the pollen extract of ragweed. Since there are several varieties of grass in pollination at the same time, the fact that these 21 patients were cured by treatment with extract of timothy pollen alone is evidence that sufficient treatment with one pollen will protect against other closely related species in the same family. This is a confirmation of observations made in a previous paper.²

Degree of Sensitivity Previous to Treatment—This varied from sensitivity to a dilution of 1:5,000 to sensitivity to a dilution of 1:80,000. There were 2 patients who reacted to a 1:80,000 dilution, 12 to 1:40,000, 19 to 1:20,000, 12 to 1:10,000 and 10 to 1:5,000. In other words, 14 patients were very sensitive, 31 had average sensitivity and 10 were moderately sensitive, as determined by extracts and dilutions made by one method.

Patient	Sex	Age at Onset	Duration, Yrs	Dilution of Pollen*	Years Treated and Result†										Results Without Treatment																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
					1923	1924	1925	1926	1927	1928	1929	1930	Dilution Sensitive\$	1933	1932	1931	1930	1929	1928	1927																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
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* T means timothy, RW, ragweed
† Dilution of pollen to which the patient reacted previous to treatment 1:20,000 means that he gave a slight reaction to that dilution in the cutaneous test, and that he gave a positive reaction to the next stronger dilution (1:10,000), and a negative reaction to the next weaker dilution (1:10,000)
‡ F means free from hay fever. P F practically free. The numbers indicate the per cent to which the patient considered himself benefited
§ Dilution of pollen to which the patient reacted the last year that he was treated

Number of Seasons Treated—With the exception of 2 patients who were treated for only two seasons, all the others were treated for from three to six seasons before it seemed justifiable to stop treatment or to call the patient cured. Four patients were treated for six successive seasons, 15 for five seasons, 23 for four seasons and 11 for three consecutive seasons. In other words, 36 of the 55 patients were cured in four or less consecutive seasons of treatment.

Decrease in Sensitivity—Of the 55 patients 3 gave a negative reaction and 12 others gave only a doubtful reaction to the whole pollen to which they had been sensitive. Previous to treatment 7 of these were sensitive to a dilution of 1 5,000, 5 to 1 10,000, 2 to 1 20,000 and 1 to 1 40,000. The number of seasons of treatment were two for 1 patient, three for 4 patients, four for 6 patients, five for 3 patients and six for 1 patient. Since the final cutaneous test was given previous to the last course of treatment, the last course of treatment should be subtracted, therefore actually all but 1 of the 15 patients gave an almost negative reaction following four or less seasons of treatment.

The reactions of 8 other patients became so nearly negative that there was no reaction to any pollen dilution, but a fairly positive reaction to the whole pollen. Two of these patients were previously sensitive to a 1 5,000 dilution and were treated for four seasons, 3 were previously sensitive to a 1 10,000 dilution and were treated for four seasons, and 3 were previously sensitive to a 1 20,000 dilution and were treated for three, four and five seasons, respectively. A deduction of the final course of treatment for the reason already stated shows that 6 of these patients reacted only to the whole pollen following three seasons of treatment, and the other 2 patients following two and four seasons, respectively.

Seven other patients showed a marked decrease in sensitivity. In 1 the dilution producing a positive reaction was changed from 1 80,000 to 1 1,000, in 2 from 1 40,000 to 1 500, and in 3 from 1 40,000 to 1 1,000. In 5 this reduction was accomplished actually by four seasons of treatment and in the other 2 by three seasons of treatment.

To summarize, the reactions of 15 patients became practically negative, 8 others gave negative reactions except to the whole pollen and 7 others showed a marked decrease in sensitivity, making a total of 30 patients in all of whom (with 1 exception) this was accomplished in four or less seasons of treatment. Contrary to this, 1 patient showed no decrease in the cutaneous reaction after two seasons of treatment, in another there was a positive reaction to a dilution of 1 10,000 instead of 1 20,000 after four seasons and in another a reaction to 1 20,000 instead of 1 40,000 after five seasons, and 2 showed a decrease of sensitivity from a positive reaction to a 1 10,000 dilution to a positive reaction to a 1 5,000 dilution after two and four seasons of treatment,

respectively. Therefore, 5 patients showed little or no decrease in sensitivity following two and four seasons of treatment in contrast to the 30 patients who showed a marked decrease.

The remaining 20 cases showed a considerable decrease in sensitivity, which was most marked in 15, in which the dilutions to which the patients were sensitive decreased as follows: in 2, from 1:40,000 to 1:500; in 4, from 1:20,000 to 1:500; in 2, from 1:10,000 to 1:500; in 1, from 1:80,000 to 1:5,000; and in 5, from 1:40,000 to 1:1,000. The actual number of seasons of treatments varied between two and four, the most frequent number being three.

Results After Omission of Treatment—All 55 patients have been free from hay fever since the omission of treatment. The number of years of freedom for the various patients is: seven years for 6 patients, six years for 18, five years for 5, four years for 18 and three years for 8. It is fair to assume that none of these patients will have a relapse, since in the former series of 100 cases only 1 patient had a relapse, and he had been treated only two seasons with no resultant decrease in sensitivity. In the present series the only patient at all similar is number 47 who was treated for three seasons with no change in the degree of sensitivity. He was, however, 51 years of age when last treated, and he has been without treatment for four more years. Patients after middle life who have had hay fever for many years are apt to experience a gradual decrease in symptoms, so that the age alone of this patient may prevent a relapse.

Comparison of Table 1 with the Previous Report—The patients in the present report were more sensitive than those reported previously, since before treatment they reacted positively to a higher dilution of the pollen extract. Probably for this reason fewer patients in this report could give an entirely negative reaction to the whole pollen, on the other hand a few in the present article showed little or no change in their sensitivity following treatment, whereas many more had only a slight reduction in sensitivity in the earlier series. In the former series 44 patients gave either a negative or only a slightly positive reaction to the whole pollen, whereas in this group of 55 there are 15, however. 8 others reacted positively only to whole pollen. In the former series 44 showed little or no change in the cutaneous reaction after treatment whereas, in the present series only 5 patients showed little or no change. Therefore, on the whole, there was a greater decrease in sensitivity in the present group than in the former group. In the former group, with the exception of 1 patient who had a return of symptoms, 22 patients have lived eight years and all the others nine years (some even longer) without a return of hay fever. Therefore it is fair to expect, since all factors are as favorable, that the present group of patients, already three or more years without hay fever, are cured.

RESULTS RECORDED IN TABLE 2

Since none of the 35 patients in table 2 were entirely free from symptoms either during or since the omission of treatment and yet are listed as apparently cured, it is necessary to qualify this statement by an explanation in each case. Patients 4, 14 and 33 were sensitive to foods, and 8 was sensitive to epidermal irritants. Patient 10 had one day of symptoms each season, and 18 had one day of symptoms resembling those of a cold in the head occasionally throughout the year. Patients 6, 9 and 26 had colds and asthma at any time of the year, and patients 7, 13, 15, 16, 21, 24, 25, 31 and 32 were subject to attacks of sneezing on rising in the morning at any time of the year. Patients 5, 28, 29, 34 and 35 had slight symptoms early in May that were likely caused by pollen of June grass, but they were free from symptoms during the late grass pollen season. Patients 3, 11, 12, 19, 20 and 23 lived in the Middle West, where they were exposed to giant ragweed, they were also sensitive to corn. Whether the treatment with small ragweed pollen did not completely protect them against the giant species or whether it was the pollen of corn or the ingestion of corn as a food that caused a little hay fever is not known, but the slight symptoms were evidence that treatment with the dwarf ragweed gave good protection against the giant variety. There is no evident excuse why the remaining 6 patients (1, 2, 17, 22, 27 and 30) were not entirely free from symptoms. The first 2 were treated for four seasons, and they have been without treatment for six years, with no increase in symptoms. The next two were treated for three and five years, respectively, and for five years have shown no increase in hay fever since the last treatment. The last 2 were treated for six and seven years, respectively, and both have now gone for four seasons without treatment and without any increase in symptoms.

Incidence, Age of Onset and Duration—In this series of 35 patients, 26 were sensitive to, and were treated with, extract of small ragweed pollen and 9 were sensitive to grass pollens and were treated with extract of timothy grass pollen. There were 22 females and 13 males. The age of onset varied between 3 and 39 years, 6 patients were more than 30 and 7 were more than 20 when the hay fever began. The duration of symptoms varied from one to thirty years, 3 patients had had hay fever for only one year, and 4 had had it for twenty years or more.

Sensitivity—Ten patients in this group were sensitive, 3 reacted to a dilution of 1:80,000 and 7 to a dilution of 1:40,000. Six patients were not very sensitive in that they reacted to a dilution of 1:5,000. The remaining 19 were sensitive to the average degree, 12 reacted to a 1:20,000 dilution and 7 to a 1:10,000 dilution.

TABLE 2—Record of Twenty-Five Patients Apparently Cured¹

Patient	Sex	Age of Onset	Duration, Years	Pollen	Dilution Sensitive	Years Treated and Result					Dilution Sensitive	Results Without Treatment				
						1924	1925	1926	1927	1928	1929	1930	1931	1932	1933	1934
1	F	30	12	RW	1 40,000±	P F	P F	P F	P F		1 1,000+	P F	P F	P F	P F	P F
2	M	39	6	RW	1 5,000+	70	P F	P F	P F		1 1,000+	P F	P F	P F	P F	P F
3	M	31	15	RW	1 40,000±	75	P F	P F	P F		1 10,000±	P F	P F	P F	P F	P F
4	F	7	1	RW	1 20,000±	50	75	P F	P F		1 500+	P F	P F	P F	P F	P F
5	F	11	5	T	1 10,000+	50	75	P F	P F		1 1,000+	P F	P F	P F	P F	P F
6	F	14	17	RW	1 20,000±	75	50	P F	P F		1 20,000±	P F	P F	P F	P F	P F
7	F	5	10	T	1 20,000±	75	50	P F	P F		1 20,000±	P F	P F	P F	P F	P F
8	F	7	3	RW	1 10,000±	70	70	75	P F	P F	P F	P F	P F	P F	P F	P F
9	F	22	3	RW	1 40,000±	50	50	75	P F	P F	P F	P F	P F	P F	P F	P F
10	M	14	30	RW	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
11	M	9	3	RW	1 80,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
12	M	13	5	RW	1 55,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
13	M	17	8	RW	1 40,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
14	M	14	5	T	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
15	M	14	5	RW	1 5,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
16	F	12	5	RW	1 5,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
17	M	8	6	RW	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
18	F	32	8	T	1 10,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
19	F	36	4	RW	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
20	M	47	8	RW	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
21	F	23	20	RW	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
22	F	22	16	RW	1 40,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
23	F	22	1	RW	1 5,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
24	F	19	3	T	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
25	M	3	13	RW	1 80,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
26	M	?	Years	RW	1 10,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
27	F	?	Years	RW	1 40,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
28	F	18	2	T	1 5,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
29	M	29	3	RW	1 10,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
30	M	23	24	RW	1 80,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
31	F	6	4	RW	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
32	F	31	1	RW	1 10,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
33	F	?	Years	RW	1 20,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
34	F	15	20	T	1 40,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F
35	F	25	3	T	1 10,000±	70	50	75	P F	P F	P F	P F	P F	P F	P F	P F

* The abbreviations are the same as for table 1

Duration of Treatment—Seven patients were treated for six seasons, 5 for five seasons, 10 for four seasons, 10 for three seasons, 1 for two seasons and 2 for only one season

Results of Treatment—Since the treatment was stopped 7 patients have gone for a period of six years, 13 for five years and the other 15 for four years without a relapse or any increase in symptoms of hay fever. These periods without treatment would seem to be long enough to justify the statement that the patients are apparently cured of hay fever, particularly with regard to the pollen with which they were treated

Variability in the Decrease of Sensitivity—Attention was not called to the variability among the patients listed in table 1 in the decrease of sensitivity resulting from treatment because it is more evident and more pronounced in the group listed in table 2. Of the 2 patients who were sensitive to a 1/80,000 dilution of pollen extract previous to treatment, 1 still reacted to a 1/10,000 dilution after three seasons of treatment and the other to a 1/5,000 dilution after six seasons of treatment, and both have gone for four years since the treatment was omitted without an increase in symptoms. Among the 6 patients who reacted to a 1/40,000 dilution of the pollen extract before treatment, 1 patient reacted to a 1/500 dilution after six seasons of treatment, 2 others reacted to a 1/1,000 dilution after four and five seasons of treatment, respectively, and for six and five years they have been without relapse, another reacted to a 1/5,000 dilution after three years of treatment and for five years has had no increase in symptoms, another's reaction decreased to only a 1/10,000 dilution after four years of treatment, and for six years he has had no relapse. Another showed no decrease in sensitivity following five years of treatment, yet this patient has had no increase in symptoms in the four years since treatment was stopped.

Comparison among the group of 9 patients, all of whom reacted to a 1/20,000 dilution of the pollen extract previous to treatment, is of interest. After six and four seasons of treatment, respectively, 2 patients reacted alike to a 1/500 dilution and have had no increase in symptoms during an interval of four and six years, respectively, 2 other patients reacted alike to a 1/1,000 dilution after five and three seasons of treatment and have been without treatment for five and four years, respectively, with no increase in hay fever, 3 others reacted to a 1/5,000 dilution after three seasons of treatment and have had no increase in symptoms without treatment for four and five years, 2 other patients showed no change in reaction to the cutaneous test following four and three seasons of treatment, respectively, and neither has had an increase in hay fever for the last six years during which no treatment has been given.

Of the 6 patients who reacted to a dilution of 1 10,000 previous to treatment, 3 patients showed no change in cutaneous reaction after three, four and six seasons of treatment, respectively, yet they have been free from hay fever for five, six and four years, respectively, since the treatment was stopped. With 2 others the reaction was diminished to positive with a 1 500 dilution after six seasons of treatment in one case and after only one season of treatment in the other, and neither has experienced an increase in symptoms during the last four years without treatment. Another patient had so nearly a negative reaction after two seasons of treatment that only the whole pollen produced a reaction, and there has been no evidence of a relapse during the four years without treatment.

There were 5 patients who reacted only to a 1 5,000 dilution previous to treatment. One still reacted to a 1 1,000 dilution after four seasons of treatment, whereas 2 others reacted only to a 1 500 dilution after three years of treatment. Of the last 2 mentioned, one has had no increase in symptoms for six years and the other for five years without treatment. The remaining 2 patients gave so nearly a negative reaction after six seasons of treatment that only the whole pollen caused a reaction, and they have had no increase of symptoms for four years without treatment.

RESULTS RECORDED IN TABLE 3

The first patient listed in table 3 reacted to extract of ragweed pollen in a dilution of 1 40,000 and received an 85 per cent benefit from treatment. The second year he was sensitive to one dilution less, and benefit from treatment was the same. The third year his sensitivity had decreased to positive reaction to a 1 10,000 dilution and following treatment he was practically free from hay fever. The fourth year duplicated the third year. In the fifth year (1926) he had no treatment and he was 75 per cent free from symptoms, the next year without treatment he was 50 per cent relieved, the third successive year without treatment he was only 25 per cent free from hay fever and the fourth year (1929) he had as much hay fever as he had had previous to treatment. The next year (1930) a test proved him to be as sensitive as he had been previous to treatment. Treatment that year gave him 75 per cent benefit and reduced his sensitivity from a reaction to a 1 40,000 dilution to a reaction to a 1 10,000 dilution, and with treatment a second season he again became practically free from hay fever.

The second patient is more striking, for during five seasons of treatment his improvement increased from 50 per cent the first season to practical freedom from symptoms for four seasons, and his sensitivity decreased from a positive reaction to a 1 20,000 dilution to a reaction to only a 1 1,000 dilution. He omitted treatment for three years, the

TABLE 3—Results Following Premature Omission of Treatment

Patient	Pollen	1922	1923	1924	1925	1926	1927	1928	1929	1930	1931
1	RW	1 40,000± 85	1 20,000± 85	1 10,000± P F	1 10,000± P F	N T 75	N T	N T 25	N T N G	1 40,000± 75	1 10,000± P F
2	RW	1 20,000± 50	1 20,000± P F	1 10,000± P F	1 5,000± P F	1 1,000± P F	N T 75	N T 50	N T N G	1 40,000± 75	1 10,000± P F
3	RW	1 80,000± P F	1 40,000± P F	N T N G	1 40,000± P F	1 40,000± P F					
4	RW	1 20,000± 75	1 10,000± P F	N T N G	N T N G	1 20,000± P F	1 10,000± P F				
5	T	1 10,000± P F	N T P F	N T N G	N T N G	1 20,000± P F					
6	RW	1 10,000± 50	1 10,000± 75	N T 50	N T 50	1 80,000± 75	1 40,000± P F	1 20,000± P F	1 10,000± P F		
7	RW	1 20,000± 75	1 20,000± P F	1 10,000± P F	N T N G	1 40,000± P F					
8	RW		1 20,000± P F	1 10,000± P F	N T N G	N T N G	1 40,000± P F				
9	RW		1 20,000± P F	N T P F	N T N G	1 40,000± 75	N T N G				
10	RW		1 20,000± 75	1 20,000± P F	1 20,000± P F	N T 75	N T 50	N T N G	1 80,000± 75	1 10,000± P F	
11	RW		1 40,000± 50	1 40,000± 50	1 20,000± P F	N T P F	N T 50	N T 25	N T N G	1 10,000± 75	
12	RW		1 20,000± 75	1 20,000± 75	N T 75	1 10,000± P F	N T 50	N T N G	1 10,000± 75		
13	RW			1 80,000± 50	1 80,000± P F	1 80,000± P F	N T P F	N T 75	N T N G	1 80,000± P F	
14	RW				1 20,000± P F	1 20,000± P F	N T P F	N T 75	N T N G	1 20,000± P F	1 20,000± P F
15	RW				1 5,000± 75	1 5,000± 75	1 1,000± P F	1 500± P F	N T N G	1 5,000± P F	1 500± P F
16	T			1 40,000± P F		N T 75	N T 75	N T N G	1 10,000± P F		
17	RW				1 160,000± 50	1 160,000± 50	1 160,000± 50	1 80,000± P F	N T 50	1 80,000± 75	1 10,000± P F
18	RW					1 40,000± P F	1 40,000± P F	1 20,000± P F	N T 75	N T 50	N T N G

* The abbreviations are the same as for table 1, with the addition of N T, meaning no treatment, and N G, meaning no benefit (symptoms as bad as before treatment)

first year he was 75 per cent relieved, the second year, 50 per cent, and the last year he had as much hay fever as he had previous to treatment. The next year (1930) his sensitiveness to the pollen extract had increased to its original extent, namely, a positive reaction to a 1:40,000 dilution. He was treated that year and received 75 per cent benefit, and the next year his cutaneous reaction had decreased to a positive reaction to a 1:10,000 dilution. Following treatment the second year he was again practically free from hay fever.

Patient 3, who reacted the first year of treatment to a 1:80,000 dilution, was practically free from hay fever. The second year of treatment his sensitivity had decreased to a reaction to a 1:40,000 dilution, and he was entirely free from hay fever. Nevertheless, following the omission of treatment the next year he had as much hay fever as he had experienced previous to treatment. The next year his degree of sensitivity by test was the same as that previous to his second season of treatment, but renewed treatment was followed by nearly complete freedom from symptoms.

Patient 5 reacted to a 1:10,000 dilution of timothy pollen extract, and the first season of treatment resulted in complete freedom from hay fever. He omitted treatment for three years during which period his relief from symptoms gradually diminished, the first year he was practically free, the second year 75 per cent free and the third year 50 per cent free. A year later (1926) he was tested and gave a positive reaction to a higher dilution (1:20,000) than he had given previous to treatment. He again became practically free from symptoms following one season of treatment, and the second season the reaction had decreased one dilution, but treatment resulted in his being again entirely free from hay fever.

Further discussion of the cases in table 3 and many more similar cases which might have been added would duplicate what has been illustrated by the few already discussed and would only verify the statements to be presented.

Only 5 of the 18 patients were as free from hay fever the first year that treatment was omitted as they were during the last year of treatment. All the others showed a relapse and the 5 had some relapse the second season without treatment. In other words, most patients who have had insufficient treatment before treatment is omitted have a relapse the first season, and the few who do not show any relapse the first year show one during the second year of omission.

Four patients showed no hay fever the last year of treatment, 3 of these were treated for two years and the other for one. In the first year without treatment 2 had as much hay fever as they had before treatment, 1 was 50 per cent better than he had been previous to treatment, and the fourth was practically free the first year of omission.

and 75 per cent relieved the second year. Three of these showed some decrease in sensitivity when the second season's treatment began. Therefore the omission of treatment after only one or two seasons of treatment, even though the last course of treatment has resulted in freedom from hay fever, is not always a safe procedure. However, in table 4 it will be shown that 15 patients have remained free from hay fever for three or more years following one season of treatment, and 23 others have done likewise following two seasons of treatment. Five patients had a complete relapse the first year that treatment was omitted, while with 8 others who had a gradual and progressive relapse it was two or three years before they experienced as much hay fever as previous to treatment.

TABLE 4—*Statistics on Preseasonal Treatment of Hay Fever for Various Periods, from 1919 to 1930*

	1	2	3	4	5	6	7	8	Total				
Number of seasons patient was treated	180	209	131	99	40	28	21	26	734				
Number of patients	15	23	61	51	26	14	0	0	190				
Number of patients permanently relieved	83	11	47	50	65	50	0	0	26				
Per cent permanently relieved	?	?	8	11	14	10	14	11	68				
Number on trial			53	61	100	86	66	40	35				
Per cent relieved			6	0	0	0	0	0	54				
Number of failures	30	18	6	0	0	0	0	0	71				
Per cent of failures	16.6	8.6	4.6	0	0	0	0	0					
Per cent of total relieved	2	4	18	26.6	22.6	20							
Per cent of total failures	4	2.4	0.8	0	0	0							
Negative reaction to pollen	6	6	8	3	1	1							
Doubtful reaction to pollen	4	4	12	8	4	1							
Positive reaction to pollen	1	1	2	10	1	3							
Positive reaction to 1:100 solution	0	2	1	1	1	2							
Positive reaction to 1:500 solution	1	0	5	5	2	3							
Positive reaction to 1:1,000 solution	0	1	2	9	6	1							
No change in reaction	2	9	21	8	4	1							
Number of years free from hay fever	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of patients free from symptoms since omission of treatment	?	?	8	31	17	25	6	22	3	40	20	8	10

Therefore, all the patients presented in table 3 began to have a relapse not later than the second season following the omission of treatment. Since all the 90 patients presented in this report have survived for three or more years (8 for only three years) without treatment and without any signs of relapse it is fair to assume that none will have a relapse.

It is of interest to note that in those whose sensitivity showed a decrease following treatment there was an increase in sensitivity during the period of omission of treatment. There was a relapse in their sensitivity as well as in their symptoms.

RESULTS RECORDED IN TABLE 4

In table 4 are presented statistics for preseasonal treatment during the interval from 1919 to 1930. No patients given treatment during the season or preceding and during the season are included. No patient

was given more than eight seasons or courses of treatment during the interval from 1919 to 1930. A total of 734 patients were treated during this period, 180 received treatment for only one season and 209 for only two seasons.

Of 180 patients treated for only one season, 15 have remained free from symptoms without treatment, 1 patient has been free for eight years without treatment, 5 for eleven years, 1 for twelve years and 4 for thirteen years. Two hundred and nine patients were treated for two seasons only, and of this number 23 have remained free from symptoms. Of the 131 patients who received treatment for only three seasons, 61 have had no relapse, of 99 treated for only four seasons, 51 have remained free from symptoms, of 40 treated for five seasons, 26 have remained free and of 28 treated for six seasons, 14 are still free from hay fever. Among the 21 and 26 patients treated for seven and eight seasons, respectively, no cures are reported. One hundred and ninety patients (100 presented in a former article and 90 here) of 734 are reported cured.

Eight per cent of those treated for one season only have remained free from symptoms, 11 per cent of those treated for two seasons, 47 per cent of those treated for three seasons, 50 per cent of those treated for four seasons, 65 per cent of those treated for five seasons, and 50 per cent of those treated for six seasons. Of the 734 patients treated 26 per cent have been free for many years since treatment was stopped. Although the greatest number of patients were cured following three and four seasons of treatment, on the percentage basis the greatest number required five seasons, and the next higher percentage was practically the same for three, four and six seasons, respectively. The statistics for the third and fourth seasons are probably the fairest because of the large number of patients that were treated for those respective seasons in comparison with the number treated for longer periods, and not many could be expected to become permanently free from symptoms following only one or two seasons of treatment. In fact, if the number treated for only one or two seasons were deducted from the total number there would remain 345 who were treated for three or more seasons, and of this number 152, or 44 per cent, remained free from hay fever for many years.

The group designated as the "number on trial," comprises the patients with whom treatment has been stopped but who, for the following reasons, cannot be counted as being permanently free from hay fever. In many, only one year has elapsed, in many others two years have elapsed, but some have failed to answer a questionnaire, and in the few remaining who have gone for a period of three years it has been impossible to establish a contact. On the assumption, which usually is true that those who have not been well would have been heard from, it may

be fair to assume that many of these patients are still free from hay fever, and this assumption is stronger in that most of these patients had been treated for from three to six seasons and the percentage of permanent relief was over 50 in such cases. The addition of these cases to the aforementioned group would increase the percentage of permanent relief (line 6, table 4) very much for each of the various periods of treatment, and the general average of permanent relief would be 35 per cent for the whole number treated. If the number of those who had treatment for only one or two years is deducted, the percentage of permanent relief would be 72.

Failure of treatment was noted in 30, or 16.6 per cent, of those treated for one season only, in 18, or 8.6 per cent, of those treated for two seasons only, in 6, or 4.6 per cent, of those treated for three seasons only, and in none of those treated for four seasons or more. The actual average of failures each season for all patients treated over a period of ten years has varied between 4 and 8 per cent. Therefore, it is evident that had those who had no relief after one season's treatment taken a second season's treatment, at least half of them would have evidenced benefit, and the same ratio would hold true for the cases of failure that followed two seasons of treatment. Those who obtained no benefit following three seasons of treatment must be regarded as showing permanent failure of preseasonal treatment. As a matter of fact, many of these patients did experience more or less benefit, but they did not think that the amount of benefit justified the expense of another course of treatment.

The percentage of permanent relief and of failure to the whole number (734) is as follows. For one season of treatment the percentage of permanent relief was 2 and of failure 4. For two seasons of treatment the percentage of permanent relief was 4 and of failure 2.4. For three seasons of treatment permanent relief resulted in 18 per cent of the total number, and failure in less than 1 per cent, there were no failures following more than three seasons of treatment, and permanent relief was obtained in 26.6 per cent, 22.6 per cent and 20 per cent following four, five and six seasons of treatment, respectively.

Following the individual season's treatment from one to six seasons inclusive, the cutaneous test was as follows. The pollen test was negative in 6 cases after one and two seasons of treatment, in 8 cases after three seasons of treatment, in 3 cases after four seasons and in 1 each after five and six seasons of treatment. The test was only doubtful in 4 cases following one and two seasons of treatment, in 12 cases after three seasons of treatment, in 8 cases after four seasons, in 4 cases after five seasons and in 1 case after six seasons of treatment. The reaction to the pollen test was positive, but not strong enough to give any reaction with a dilution in 1 case following one, two and five seasons of treatment,

respectively, in 2 cases after three seasons of treatment, in 10 cases after four seasons of treatment and in 3 cases after six seasons of treatment. Seven patients had a positive reaction to a 1:100 dilution only, after various seasons of treatment, 16 to a 1:500 dilution and 19 to a 1:1,000 dilution, and 45 patients of the cured showed no change in cutaneous reaction. The remaining 20 odd cases showed more or less change. Thus, 58 patients gave either a negative or a practically negative reaction, 18 a reaction only with the whole pollen and 23 a reaction only with the strongest dilutions, 45 showed no change in the cutaneous reaction, and the remaining 40 odd cases showed from little to considerable change at the time treatment was stopped. Eight patients have been free from hay fever for three years, 32 for four years, and so on for increasing lengths of time up to thirteen years for 10 patients. In fact, 78 of the 190 patients have been free from hay fever for ten or more years since treatment was omitted.

SUMMARY

The patients were treated preseasonally, at weekly intervals, over a period of fifteen weeks, or for a period, determined by cutaneous tests with various dilutions of pollen extract, that would usually insure two or more treatments with a 1:500 dilution of the pollen extract just prior to the usual onset of symptoms of hay fever. The pollen extract that was used was in physiologic solution of sodium chloride enforced with alcohol.

In table 1 the records of 51 patients are presented, all of whom have been free from hay fever for periods ranging from three to seven years. Only 8 patients have been free for as short a time as three years, 18 for as long a time as four years, 5 for five years, 18 for six years and 6 for seven years. With the exception of 2 patients who were treated only two seasons and 4 who were treated for six seasons, all patients were treated for from three to five successive seasons, 15 were treated for five seasons, 23 for four seasons and 11 for three seasons. At the end of treatment the cutaneous reaction to the pollen became negative or only doubtfully positive in 15 patients, in 10 others there was only a fair positive reaction to the pollen and in all the remaining cases varying degrees of lessened sensitivity were shown, from a slight to a marked decrease. Previous to treatment 14 were very sensitive, 19 showed average sensitivity and the remainder were moderately sensitive. The cases were equally divided between the two sexes, 34 were due to ragweed pollen, and 21 to timothy pollen. The age of onset of hay fever varied from 1 year to 57, and the duration of hay fever varied from one to thirty years.

In table 2 are the records of 35 patients, none of whom is classed as entirely free from hay fever, but all are described as practically free

As a matter of fact, all these patients are probably entirely free from symptoms of hay fever caused by the pollens with which they were treated, in fact, the slight symptoms in evidence during the pollen season were, in most cases, as pronounced at other times of the year. In this group were a few more females than males, and a few more patients were sensitive to and treated with ragweed than with timothy pollen extract. The age of onset, the duration of hay fever and the degree of sensitivity in this group resembled those recorded in table 1. Seven patients were treated for six successive seasons, 5 for five seasons, 10 for four seasons, 9 for three seasons and 2 for one season only. The duration of treatment in this group was considerably shorter than in the former group, and the decrease in sensitivity after treatment was likewise less marked, but to offset this these patients have been without treatment for a longer time without an increase in symptoms than the former group. Fifteen have gone for four years, 13 for five years and the remaining 7 for six years without an increase in symptoms. In case of doubt as to the permanency of the treatment attention is called to a former paper² which included 14 similar cases, 8 of the patients have been without treatment for ten years without an increase in symptoms, and their sensitivity to the pollen extract was not markedly reduced, and the other 6 patients, in whom the sensitivity was greatly reduced following treatment, have had no increase in symptoms during an interval of seven years.

In table 3 are presented a group of patients who illustrate the disastrous results of stopping treatment prematurely. Some patients have a complete relapse the first season that treatment is omitted, others have a gradual relapse beginning the first year, and the few who may be as free from symptoms the first year that treatment is omitted begin to have a relapse not later than the second season. The individuality of the patients so complicates any rules that may be promulgated with regard to the curability of hay fever and the amount of treatment necessary that the best guide would seem to be the experience of the physician.

Table 4 is a composite of a former paper² and the present one, giving statistics on all the patients with pollen hay fever (734) whom I have treated preseasonally during the interval from 1919 to 1930. One hundred and eighty patients received treatment for only one year. Of this number 15, or 8 per cent, have been free from hay fever, in 6 cases the pollen reaction became negative, in 4 others it was doubtful, in 2 there was no change, and in 2 there was a marked decrease. There were 30, or 16 per cent, in whom treatment failed. Among the 209 patients who were treated only two seasons, 23, or 11 per cent, have remained free from hay fever, in 6 the pollen reaction became negative, in 4 others it was only doubtful, in 9 there was no change, and the remaining 4 showed a marked decrease. There was failure in 18,

or 8 per cent. In the group of 131 patients who were treated for three seasons, 61, or 47 per cent, remained free from hay fever, in 8 the pollen reaction became negative, in 12 others it became only doubtful, in 21 there was no change, and in the remaining patients the decrease in sensitivity varied from little to marked. If the 8 additional patients who are on trial continue without treatment to be free from hay fever, as is expected, they will raise the number of those permanently relieved to 69 and the percentage of the groups having had treatment for three seasons to 53. Six, or 4 per cent, failed to be relieved.

Among those treated for four seasons only there were no failures, and 51, or 50 per cent, have remained free from hay fever, if the 11 others on trial continue to be free the percentage will be increased to 61. In 3 of this group the reaction to the pollen test became negative, and in 8 only doubtful, 10 gave a positive reaction only with the whole pollen, 8 showed no change, and the others showed from a little to a marked change. The two groups of patients treated for five and six seasons showed the highest percentage of permanent relief, namely, 65 and 50, respectively, and if those on trial are included the total would be 186, respectively. However, the total number of patients in these two groups was relatively small. The decrease in sensitivity was relatively less.

In the two groups of patients treated for seven and eight seasons, respectively, none is permanently relieved, and the cutaneous tests have not been markedly changed by treatment. However, 14 and 11 patients in these respective groups are on trial without treatment and are expected to remain permanently free from hay fever.

Therefore, of the 734 patients who received treatment preseasonally for various periods ranging from one to eight seasons, 190, or 26 per cent, have remained free from hay fever. To this number might be added 68 more who are on trial, and who are anticipated to remain free from hay fever, to make the total 258, or 35 per cent. All failures occurred after treatment for one, two or three seasons. Since the largest number of failures occurred after one season of treatment, only half as many after the second season and half as many after the third season as after the second, it is evident that many failures following one season of treatment would result in benefits after a second season, and the same for the third season, provided treatment was continued. The largest number and likewise the highest percentage of cases of permanent relief followed treatment that was given for three, four, five and six successive seasons. The most marked diminution in the cutaneous reaction occurred in these groups, although the patients who were treated only one or two seasons ran a close second.

Of the 190 patients who have remained free from hay fever since the omission of treatment, 8 have been free for three years, 31 for four

years, 17 for five years, 25 for six years, 6 for seven years, 22 for eight years, 3 for nine years, 40 for ten years, 20 for eleven years, 8 for twelve years and 10 for thirteen years, and all are still free from hay fever

CONCLUSIONS

Preseasonal treatment for hay fever offers a cure, provided that the proper pollen extract is used, careful tests are made and judgment is employed in the manner of treatment

Permanent relief is obtained in between 26 and 35 per cent of all those who are preseasonally treated. A deduction of those who take treatment for only one or two years would increase the percentage to 44. A few patients are cured following only one or two seasons of treatment. The majority of cures, however, result from three, four, five and six successive seasons of treatment. The percentage of yearly failures varies between 4 and 7, therefore, another 50 per cent receive benefit, and this benefit averages more than 75 per cent relief.

Privately made, individual pollen extracts used in a locality in which the pollen flora is not very diversified undoubtedly facilitated these results.

NOTE —Although these patients were treated in private practice the pollen extracts were made by the author in the medical laboratory of the Peter Bent Brigham Hospital. These same extracts and the same methods of testing and treatment are employed in the outpatient department of that hospital.

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MODIFYING ACTION OF CALCIUM AND SODIUM BICARBONATE ON SALICYLATE INTOXICATION

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AND

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In an investigation of the properties and pharmacologic action of calcium acetylsalicylate¹ there were indications of certain advantages that this salt had over acetylsalicylic acid. It appeared to be less toxic, particularly with reference to the induction of albuminuria. However, calcium acetylsalicylate proved to be unstable, and the present inquiry was undertaken to determine whether a mixture of a calcium salt with acetylsalicylic acid would be correspondingly less toxic than acetylsalicylic acid alone.

Eighteen normal healthy dogs were selected which after repeated examination were proved to have albumin-free urine (Heller's test). Each dog received 100 mg of acetylsalicylic acid, U S P, per kilogram three times a day in gelatin capsules. One group of six dogs received, in addition, an equal amount of calcium gluconate, and another group of six an equal amount of sodium bicarbonate, chemically pure. The dogs were watched carefully for (1) vomiting, (2) albuminuria, (3) the development of what are here called toxic symptoms, namely, marked anorexia, asthenia, staggering gait, visual disturbances or convulsions, and (4) death. Two dogs from each group were killed after ten days' administration for autopsy and histologic examination of tissues (when any doses given were vomited, they were readministered until retained). The essential findings are recorded in the accompanying table.

As indicated in the table, all dogs vomited at approximately the same time, and from a dose of approximately the same amount of acetylsalicylic acid, i e., an average of from 0.58 to 0.63 Gm per kilogram. There was no significant modifying influence by either calcium gluconate or sodium bicarbonate. This is in contrast to the evidence of gastric irritation exhibited at autopsy in the animals at death or when killed. As will be reported in more detail later, the dogs receiving

This study was aided by a grant from the Mark H Wodlinger Fund.

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¹ Thompson, H E., and Dragstedt, C A. The Chemical and Pharmacological Properties of Calcium Acetylsalicylate, *J Am Pharm A* **22** 1096, 1933.

*Observations on Eighteen Dogs**

Day	Total Given per Kg	Acetylsalicylic Acid Alone						Acetylsalicylic Acid with Calcium Gluconate						Acetylsalicylic Acid with Sodium Bicarbonate					
		3	4	8	10	17	18	1	2	7	9	15	16	6	11	12	5	13	14
1	01																		
	02																		
	03	A																	
2	04														V				
	05		V			V		V	V	V	V						AV	V	
	06	V		A	A						A					V			V
3	07			V			V					V	V						
	08			T	V	A	A												
	09																		
4	10		A					A											
	11	TD																	
	12													V					
5	13																		
	14		T												A				
	15							T											
6	16																		
	17																		
	18																		A
7	19																		
	20																		
	21							D				A†	ATD						
8	22			D		T													
	23																		
	24																		
9	25																		
	26																		
	27																		
10	28																		
	29																		
	30					K	K					K	K				K	K	
11	31																		
	32																		
	33																		
12	34																		
	35															A			
	36																		
13	39				T														
14	42															T			
15	45								A		T								
16	48																		
17	51																		
18	54				D														
19	57																		
20	60†																		
21	64										D								
22	68							T											
23	72									T									
24	76									A									
25	80									D									
26	84								D										
27	88		D																
28	92																		
29	96																		
30	100																		
34	116																		
35	120†															D			
45	150														T				
															D				

* A stands for albuminuria, V for vomiting, K for killed, T for signs of toxicity, and D for death

† Bronchial pneumonia

‡ Dose increased

acetylsalicylic acid alone showed considerably more gastritis and ulceration than either of the other groups. The explanation, we believe, is that the vomiting induced by the type of administration here employed is due to the systemic action of the salicylate. This is likewise indicated by the observation that in all dogs after the initial appearance of vomiting on the second to the fourth day, it did not recur, so that a certain degree of tolerance on the part of the center for vomiting seems to have developed. We have reported elsewhere¹ that single large doses of acetylsalicylic acid (1 Gm per kilogram) will produce immediate vomiting, presumably owing to local irritation.

With respect to the production of albuminuria there is a definite difference between the three groups of dogs. With acetylsalicylic acid alone albuminuria appeared after doses of 0.3, 1, 0.6, 0.6, 0.8 and 0.8 Gm per kilogram, respectively, for an average of 0.68 Gm per kilogram. Albuminuria had developed in all dogs by the time 1 Gm per kilogram had been given, and this continued throughout the remainder of the experiment. When calcium gluconate was administered simultaneously, albuminuria appeared after doses of 1, 4.3, 7.6, 0.6 and 2.1 Gm per kilogram, respectively, for an average of 3.12 Gm, and in one of the dogs killed it had not appeared after 3 Gm per kilogram had been given. Thus in this series albuminuria developed in only two of six animals when 1 Gm per kilogram had been given, and the albuminuria was not marked or constant until shortly before death. In the series receiving sodium bicarbonate, albuminuria appeared after doses of 2.1, 1.4, 3.5, 0.5 and 1.8 Gm per kilogram, respectively, for an average of 1.8 Gm, while it had not appeared in one dog sacrificed after receiving 3 Gm per kilogram. Here, albuminuria had developed in only one of the six animals when a dosage level of 1 Gm per kilogram had been reached. While the number of animals tested is comparatively small, it seems apparent that there is a distinctly diminished tendency for acetylsalicylic acid to provoke albuminuria when either sodium bicarbonate or calcium gluconate is simultaneously administered. The histologic observations to be reported later are in harmony with this observation. There was distinctly more renal damage in the group of dogs receiving acetylsalicylic acid alone than in either of the other two groups. There is considerable conflict in the literature as to the modifying effect of sodium bicarbonate on salicylate albuminuria both in the experimental animal and in man (Hanzlik²). We have found nothing in the literature relative to calcium in this respect other than the comment by Cantarow³ that the administration of calcium has been found

² Hanzlik, P. J. *Actions and Uses of the Salicylates and Cinchophen in Medicine*, Baltimore, Williams & Wilkins Company, 1927.

³ Cantarow, A. *Calcium Metabolism and Calcium Therapy*, Philadelphia, Lea & Febiger, 1931.

beneficial in certain cases of adolescent albuminuria. There is no indication from our experiments as to its mode of action in this regard.

Objective signs of toxicity, such as marked anorexia, asthenia, staggering gait, visual disturbances or convulsions, occurred in the dogs receiving acetylsalicylic acid alone after the total doses administered had reached 11, 14, 08, 38, and 22 Gm per kilogram, respectively, while they had not appeared in one of the dogs killed after administration for ten days. Thus toxic symptoms were seen in four of the six dogs when the total dose administered was 3 Gm. In the group receiving calcium gluconate toxic symptoms developed after doses of 15, 68, 69 and 43 Gm per kilogram, respectively, while neither of the two dogs killed at the ten day period had exhibited them. Thus only one of six dogs in this group showed toxic symptoms by the time 3 Gm per kilogram had been administered. In the sodium bicarbonate group toxic symptoms developed after doses of 21, 12 and 4 Gm per kilogram, respectively. Neither of the two dogs killed on the tenth day had shown toxic symptoms, nor did one dog to which acetylsalicylic acid and sodium bicarbonate were administered until 50 Gm per kilogram had been given, when the administration was stopped. Thus only one of six dogs in this group showed toxic symptoms by the time 3 Gm per kilogram had been given. We are unable to account for the extreme degree of tolerance manifested by one dog in this series. Toward the end of the period of administration in this animal the daily dose was increased to 09 Gm per kilogram a day without untoward symptoms. The corresponding times of death of all animals are indicated in the table. It is noteworthy that the appearance of vomiting did not usher in the other objective symptoms of toxicity. In practically all the clinical reports on salicylate intoxication vomiting is reported as appearing first, the other toxic manifestations appearing later but not as conspicuously so as in this experiment. There is, however, somewhat more correlation between the appearance of albuminuria and the toxic symptoms except in the one dog in the group receiving sodium bicarbonate which had unusual tolerance of the toxic effects. This dog showed persistent albuminuria for three months without toxic symptoms appearing at any time.

These experiments represent a parallel to an intensive type of salicylate medication. Such intensive methods are frequently employed clinically for a short period to accomplish what may be called salicylization, at which time the medication is temporarily halted or reduced. In our experiments the medication was continued at a high level in order that the effects of the simultaneous administration of sodium bicarbonate or calcium might be more readily appreciated. We interpret the results reported here as indicating a distinctly appreciable ameliorating effect on the albuminuria and toxic symptoms of salicylism with

both of these agents. Much has been written about the value of alkali therapy in salicylate medication. Hanzlik² said that it had no beneficial effect. Other recent writers (Morris and Graham⁴) have defended its use. In most instances the rationale of its employment has been to prevent the development of acidosis as a sequel to salicylate therapy or to reduce the local gastric irritation. We did not attempt to determine the acid-base balance in our experiments. The results reported here together with those reported previously with calcium acetylsalicylate¹ indicate that calcium likewise has some protective influence on the development of salicylism. The mode of this action is not clear. It may be similar in character to the protective action of calcium against carbon tetrachloride poisoning described by Minot and Cutler⁵.

CONCLUSIONS

The ameliorating influence of sodium bicarbonate on certain of the untoward symptoms produced by salicylate medication reported by many workers is confirmed in these experiments. Simultaneous administration of calcium (in the form of calcium gluconate with acetylsalicylic acid) was found to have a similar and in certain respects a greater ameliorating effect.

4 Morris, N., and Graham, S. The Value of Alkali in Salicylate Therapy, *Arch Dis Childhood* **6** 273, 1931.

5 Minot, A. S., and Cutler, J. T. Guanidine Retention and Calcium Reserve as Antagonistic Factors in Carbon Tetrachloride and Chloroform Poisoning, *J Clin Investigation* **6** 369, 1928.

Book Reviews

Bacterial Infection By J L T Appleton Price, \$7 Pp 637, with 122 engravings and 4 colored plates Philadelphia Lea & Febiger, 1933

The second edition of this book has been completely revised, and nearly two hundred pages have been added to the text, including new chapters on oral manifestations of extra-oral infections, several chapters on periapical infection and a chapter on oral hygiene. The sequence of chapters has been changed, and some material has been deleted.

The book is divided into three parts. The first, dealing with bacteriology, endeavors to acquaint the reader with the fundamental information on the morphology, physiology and ecology of bacteria. The second part deals with infection and oral hygiene, while the third deals with infection of the oral cavity. The author has made considerable use of current literature, there are references at the bottom of almost every page. The illustrations are, for the most part, from the work of others, these are carefully selected and are pertinent to the subject matter. One or two, such as figure 59, might well be omitted or might be better executed.

Most of the book deals with general phases of bacteriology and immunity, without any relation to the dental field, and in that respect does not differ greatly from the standard textbooks on bacteriology. Of necessity, the descriptions of bacteria and even of the theoretical considerations of infection and immunity are brief, suggesting that perhaps too much material is covered to make an altogether satisfactory presentation. Naturally, the chapters dealing with the bacteriology and infection of the oral cavity are the most important, since one does not find many textbooks dealing with this phase of the subject. The discussion of the treatment and control of periapical infections is particularly important and embraces the present knowledge of the subject.

The book will be of considerable value to dental students and to dentists who desire a reference work in this field.

I reumatismi cronici By Dott Riccardo Arrigoni Pp 344, with 23 illustrations Pisa Casa Editrice U Giardini, 1933

This is an excellent monograph on chronic rheumatic diseases. The author has availed himself of the literature from all possible sources and likewise presents and discusses cases of his own. Thus he combines the opinions of others with his personal experiences and observations.

An introduction, which describes the wide prevalence of these diseases among civilized peoples and the disability and suffering occasioned by them, as well as the economic losses each year, is short and to the point. The language in which this book is written is simple but forceful.

In the first third of this volume the author discusses rather thoroughly the various etiologic factors, both predisposing and exciting. Each factor is carefully

considered from practically every point of view. The last two hundred pages are devoted to an excellent presentation of case histories, with a discussion of studies of the blood and roentgen findings, as well as histopathologic studies. The roentgenograms and photomicrographs add considerably to the interest of this splendid volume, which is probably the best treatise on the subject of chronic rheumatic diseases yet published.

HYPERPARATHYROIDISM DUE TO DIFFUSE HYPERPLASIA OF ALL PARATHYROID GLANDS RATHER THAN ADENOMA OF ONE

CLINICAL STUDIES ON THREE SUCH CASES

FULLER ALBRIGHT, M D

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AND

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The literature now contains over 100 cases of hyperparathyroidism proved by autopsy or operation. At the Massachusetts General Hospital we have studied 19 such cases. Our experience with the first 14 of these cases led us to believe that the pathologic basis of this condition is a functioning adenoma of one parathyroid gland, or possibly on rare occasions of two glands, with the remaining glands relatively normal (fig 1).¹ The vast majority of the cases in the literature supported this belief.

Cases 15, 16 and 17 in our series, however, demonstrate conclusively that the parathyroid pathologic process in some instances is entirely different, namely, a hyperplasia of all parathyroid tissue. This constitutes a different disease, which it is important to recognize and which requires different treatment.

REPORT OF CASES

CASE 15—A P, a widow of 62, entered the hospital for the third time in November 1933, with the diagnosis of renal calculi. She stated that she had "always been a large water drinker." She first noticed the occasional passage of gravel with urination about seven years previously. Her first admission in 1928 was because of bilateral renal calculi. Two stones were removed from the right kidney pelvis. Her past history at that time showed no suggestion of bone involvement except that her teeth had been removed about fifteen years previously because of "rheumatism." She had had rheumatic fever as a child. Seventeen years before this admission she had had gallstones removed. The menopause occurred in 1923. She had two children.

Read before the Society of Clinical Investigation at Atlantic City, N J, on April 30, 1934.

From the Medical, Pathological and Surgical Departments of the Massachusetts General Hospital.

¹ Albright, F, Aub, J C, and Bauer, W. Hyperparathyroidism. A Common and Polymorphic Condition as Illustrated by Seventeen Proved Cases from One Clinic, J A M A **102** 1276 (April 21) 1934.

Her second admission was noncontributory

On her third admission, in November 1933, bilateral renal calculi were again found. The positive findings on physical examination were edentia, rheumatic heart disease with mitral stenosis and auricular fibrillation and a slight cystocele and rectocele. The nonprotein nitrogen content of the whole blood was 32 mg per hundred cubic centimeters. The urine showed many white cells but was otherwise not remarkable. The excretion of phenolsulphonphthalein was only slightly impaired. A stone was removed at operation from the left ureter.



Fig 1—Photomicrograph of a small parathyroid adenoma in patient 2 of the series reported by Albright, Aub and Bauer,¹ illustrating the situation which exists in most cases of hyperparathyroidism, namely adenoma formation. The adenoma is so small that the normal parathyroid tissue with its honeycombing of fat cells can be seen as a crescent at the periphery.

Routine serum calcium and phosphorus determinations were done as on all patients with renal calculi. The values found were 15 and 2.2 mg, respectively, per hundred cubic centimeters, these were checked at 13.9 and 2.2 mg. It appeared probable, therefore, that the stones were due to hyperparathyroidism.

Roentgenographic studies failed to show evidence of skeletal involvement. This fitted the fact that the serum phosphatase was only slightly elevated, 7.3 Bodansky units.

On December 19, the neck was explored (E D C) Almost at once a parathyroid tumor, measuring 1.5 by 1.2 by 0.5 cm, was found below the right lobe of the thyroid. The dissection was carried to the left side, and another tumor (1.8 by 0.8 by 0.6 cm) was found in a position symmetrical with that of the first. Both tumors were removed. The dissection was not carried further (fig 2A).

This was the first patient in our series in whom more than one tumor was found. The postoperative course was followed with some anxiety, in anticipation

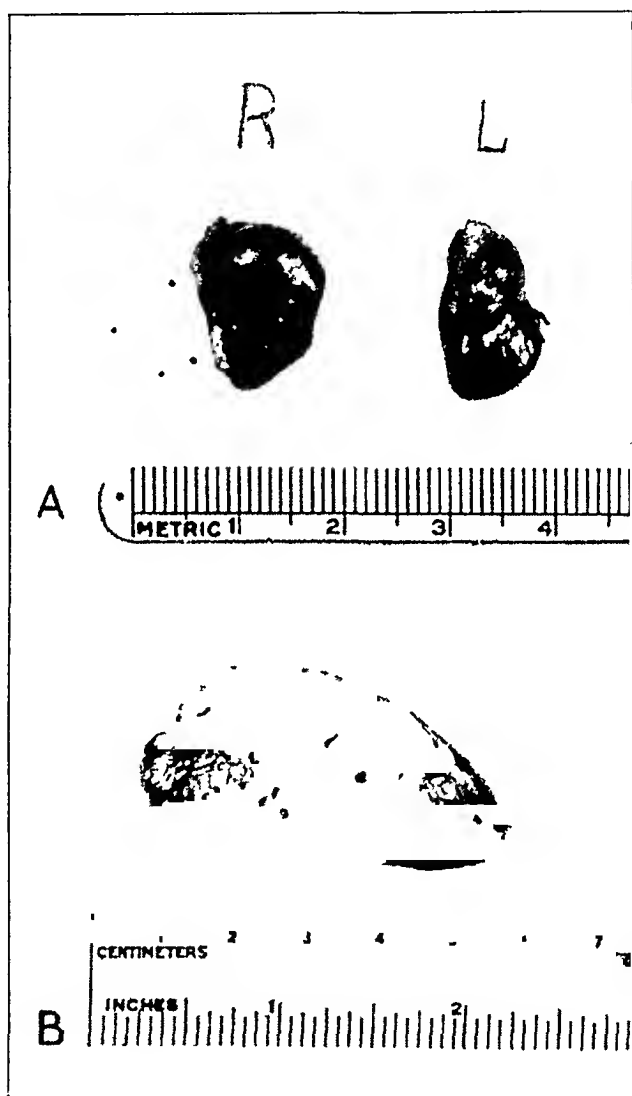


Fig 2—A, parathyroid glands removed from A P at the first operation
B, a parathyroid gland removed from A P at the second operation

of severe tetany. Much to our surprise no signs of tetany appeared, and the serum calcium and phosphorus values seven days after operation were found to be 15.4 and 2.2 mg, respectively. It then seemed probable that the patient had at least one more tumor and that we had been dealing with hyperplasia of all four parathyroid glands. This point of view was strengthened when the histologic structure of the two tumors was found to be different from that in the first 14 cases in the series.

A second operation was performed on Feb 28, 1934. In spite of a thorough search, the left upper parathyroid gland was not demonstrated. The right upper gland was easily found lying behind the esophagus and extending into the posterior mediastinum. It measured 5 by 3 by 1.3 cm. It was resected, a piece of gland about twice the size of a normal gland being left in place (fig 2 B). Following this operation there was a definite change in the blood calcium and phosphorus values (table 1).

CASE 16—T. F., a truck driver of Irish descent, single, aged 26, entered the urologic service in October 1933 because of right renal colic. He had had intermittent attacks for fifteen months. Polyuria, polydipsia and nocturia (urination three or four times each night) had been present for one year or so. Physical examination was noncontributory. The roentgenogram showed two small stones in the right ureter. The phenolsulphonphthalein excretion was normal, as was

TABLE 1—*Preoperative and Postoperative Serum Calcium and Inorganic Phosphorus Values for A. P.*

Date	Calcium, Mg per 100 Cc	Phosphorus, Mg per 100 Cc	Phosphatase, Bodansky Units	Comment
11/29/33	15.0	2.2		
12/4/33	13.9	2.2		
12/11/33			4.5	
12/19/33				First operation
12/26/33	15.4	2.2		
1/9/34	14.1	1.7		
1/22/34	13.7	1.9		
1/29/34	13.7	2.3	7.5	
2/3/34	13.8	1.9	5.7	
2/27/34	14.0	2.3		
2/28/34				Second operation
3/3/34	13.3	2.2		
3/7/34	12.0	2.2		
4/11/34	11.4	2.2		
6/7/34	15.1	2.7		
6/22/34	13.8	2.8		
6/25/34	13.6	2.7		

the nonprotein nitrogen level in the blood. The urine at that time was reported as normal. The stones were removed at operation.

The routine test for serum calcium and inorganic phosphorus showed these values to be 15.1 and 1.8 mg per hundred cubic centimeters.

The diagnosis of hyperparathyroidism was clear. Roentgenograms of the bones showed no evidence of bone disease, which corresponded with the fact that the patient had had no symptoms referable to such involvement. Further examinations of the urine showed it to be loaded at times with fine granular casts of a type which we now associate with hyperparathyroidism.²

Operation was performed on Feb 16, 1934. A parathyroid tumor, measuring 1.5 by 1 by 0.6 cm, was found below the right pole of the thyroid at the sterno-clavicular junction. This was removed. Directly beneath this was a second, much larger tumor that lay on the surface of the prevertebral fascia and the posterolateral aspect of the trachea and esophagus, anatomically it could well have been a tumor of the right superior parathyroid body descending on the deep plane of fascia. This likewise was removed. It measured 4.5 by 3.5 by 2.5 cm.

² Albright, F. and Bloomberg, E., to be published.

The histologic structure of the two tumors was identical and similar to that of the three tumors in case 15 and dissimilar from that of the tumors in our first 14 cases

The preoperative and postoperative serum calcium and phosphorus values are shown in table 2

CASE 17—J M M, a married woman of 55, entered the urological service on Dec 1, 1933, with the diagnosis of right ureteral calculus. Right renal colic had developed fourteen months previously, and she had had intermittent attacks since that time. There was no history of polyuria, polydipsia or passage of gravel.

The past history showed syphilitic periostitis diagnosed in 1927, for which she had had adequate treatment. At the age of 36, one pregnancy terminated with a miscarriage at six months. An uneventful menopause occurred six years before admission. There was no history of symptoms related to involvement of the skeleton. Her teeth had all been removed twenty-five years previously because of "decay." She ate little meat and drank almost no milk.

The physical examination revealed little of importance. The blood pressure was 170 systolic and 95 diastolic. She was moderately obese.

TABLE 2—*Preoperative and Postoperative Serum Calcium and Inorganic Phosphorus Values for T F*

Date	Calcium, Mg per 100 Cc	Phosphorus, Mg per 100 Cc	Comment
2/14/34	15.4	2.6	High calcium, high phosphorus diet
2/15/34	15.3	2.9	
2/16/34	16.0	2.5	Operation
2/17/34	11.9	2.6	
2/19/34	11.7	2.5	
2/28/34	10.8	2.2	
4/13/34	10.2	2.3	

Roentgen examination of the kidneys with iodopax revealed bilateral double ureters with a stone in one of those on the right. The heart was enlarged, and there was calcification in the aortic knob.

The renal function, as judged by the fractional phenolsulphonphthalein excretion, was normal. The urine showed white cells and red cells. The nonprotein nitrogen content of the blood was 31 mg per hundred cubic centimeters. The Wassermann reaction was positive and later negative.

The stone was removed on December 5.

The routine determinations of serum calcium and inorganic phosphorus showed a calcium content of 12.7 mg and a phosphorus content of 2.4 mg; these were checked at 14 mg and 3 mg. The serum phosphatase was 42 Bodansky units, a normal figure, which supported the clinical impression that there was no bone disease. The diagnosis of hyperparathyroidism seemed assured.

Special roentgenograms of the skeleton failed to demonstrate skeletal disease.

The parathyroid region was explored. Four parathyroids were found at the four poles of the thyroid. All were greatly enlarged. Three of the glands were removed, leaving the right upper one, from which a small bit was taken for histologic examination.

The weights and dimensions of the glands removed were as follows: left upper, 2 Gm, 2 by 2 by 1 cm; left lower, 0.6 Gm, 1 by 0.8 by 0.4 cm; right lower, 0.8 Gm, 1.8 by 1.2 by 0.4 cm.

The histologic structure of these four glands was similar to that of the three glands removed in case 15 and the two glands removed in case 16. The preoperative and postoperative serum calcium and inorganic phosphorus values are given in table 3.

HISTOLOGY

A histologic study of the parathyroid tissue removed in these 3 cases reveals two important facts. In the first place, the microscopic picture is everywhere similar in the different glands of the same patient and in those of the different patients; in the second place, it is entirely different from that seen in the other 16 cases (figs. 3, 4 and 5).

Although the single tumor nodules are very variable among themselves as regards histologic structure, the following brief composite description will be given for comparison. A more complete report of the study of the morphology of both types of tumors is being prepared by one of us (B. C.).

TABLE 3—*Preoperative and Postoperative Serum Calcium and Inorganic Phosphorus Values for J. M. M.*

Date	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Comment
12/ 3/33	12.7	2.4	Serum phosphatase, 4.2 Bodansky units Operation
12/11/33	14.0	3.0	
2/ 3/34	12.4	2.1	
2/14/34			
2/15/34	10.9	2.2	
2/17/34	10.8	2.2	
3/ 6/34	11.3	2.8	
3/22/34	10.8	3.1	
4/ 3/34	10.5	3.1	
6/ 9/34	10.7	3.0	
6/20/34	10.2	3.1	
6/25/34	10.6	3.0	

The single tumors are usually composed of hyperchromatic chief cells, slightly larger than the normal chief cell. Occasionally these cells are twice the normal size and are multinucleated. No mitotic figures are seen. The cells are arranged in columnar, glandular or pseudo-glandular formation and often show definite palisading. In addition to the pure chief cells, there are often cells with water-clear cytoplasm (*wasserhellen Zellen*). The latter are larger than the chief cells and have more sharply demarcated cell membranes, and their cytoplasm is practically nonexistent owing to vacuolation. Such cells have a tendency to arrange themselves in circumscribed, closely packed, nonalveolar groups of varying sizes, but only in rare instances do they comprise most of the specimen. Transition forms between the chief and the water-clear cells are met with in many cases. Finally, as in the normal parathyroid, almost all of the single tumors contain oxyphil cells, either singly or in groups of varying size. The two other important differences from the normal are the increased vascularity and the decrease or absence of fat cells.

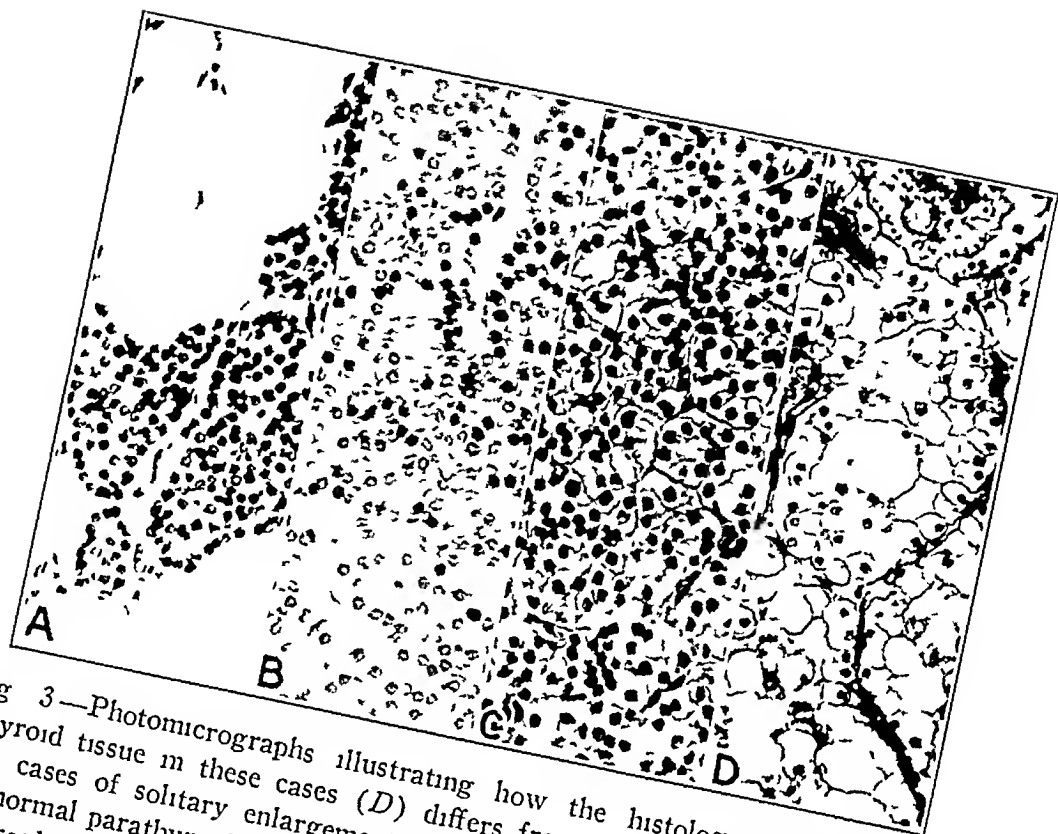


Fig 3—Photomicrographs illustrating how the histologic structure of the parathyroid tissue in these cases (D) differs from normal tissue (A), and from that in cases of solitary enlargement of the parathyroid glands (B and C). A shows normal parathyroid tissue. Note the honeycombing with fat cells. B shows parathyroid tissue from a case of solitary enlargement made up of chief cells. C shows parathyroid tissue from a case of solitary enlargement in the transition stage to *wasserhellen* cells. D shows parathyroid tissue from A.P. Note the size of the cells, the clearness of the cytoplasm and the tendency to gland formation.

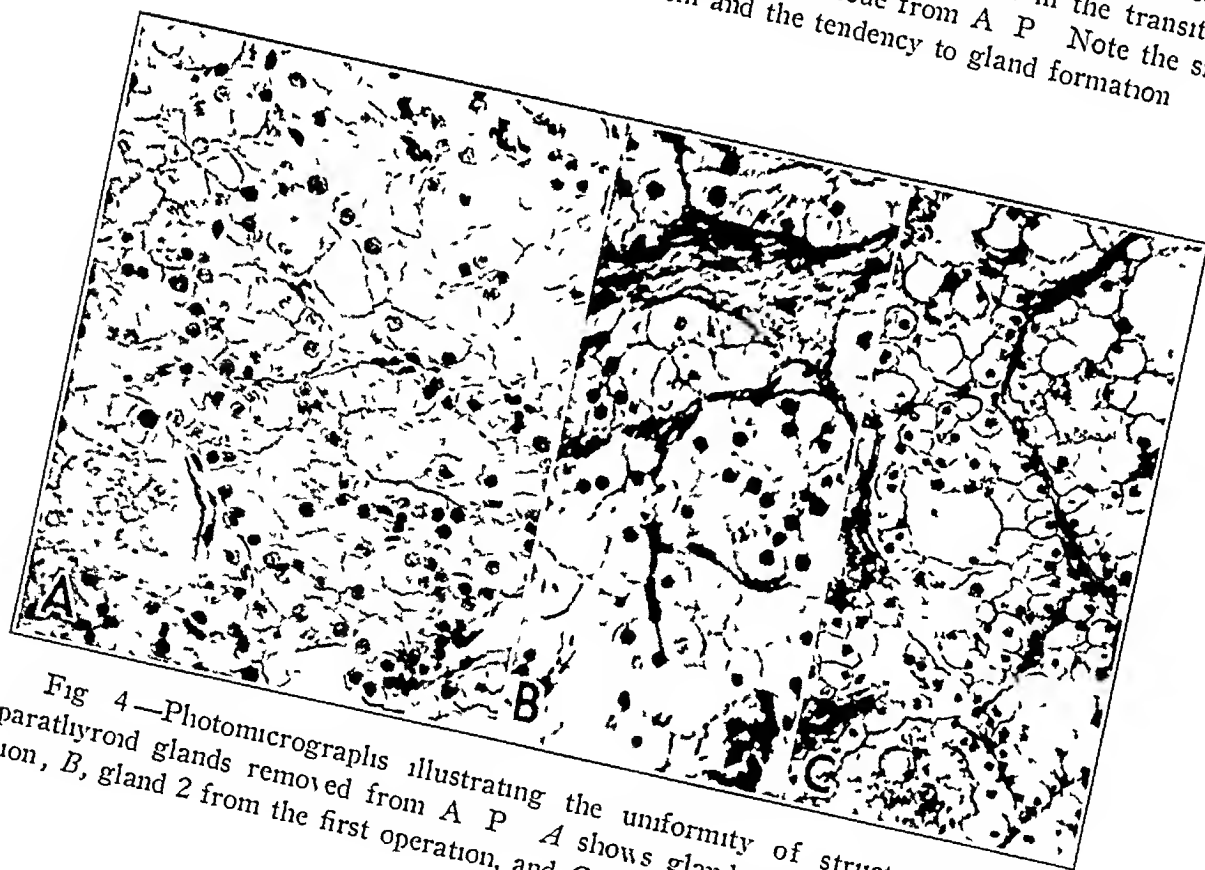


Fig 4—Photomicrographs illustrating the uniformity of structure in three parathyroid glands removed from A.P. A shows gland 1 from the first operation, B, gland 2 from the first operation, and C, a gland from the second operation.

In the glands from the 3 cases of multiple enlargements reported here the cells are all of the same type, a *wasserhelle Zelle* which is much larger than the same type of cell as it occurs in the solitary tumors. Furthermore, there is an increased tendency to glandular arrangement. Fat tissue is absent. There is almost no intracellular fat. Oxyphil cells, chief cells and mitotic figures are absent. The homogeneity of structure, the size of the cells, the clearness of the cytoplasm and the tendency to glandular formation, however, are the features which characterize this condition.

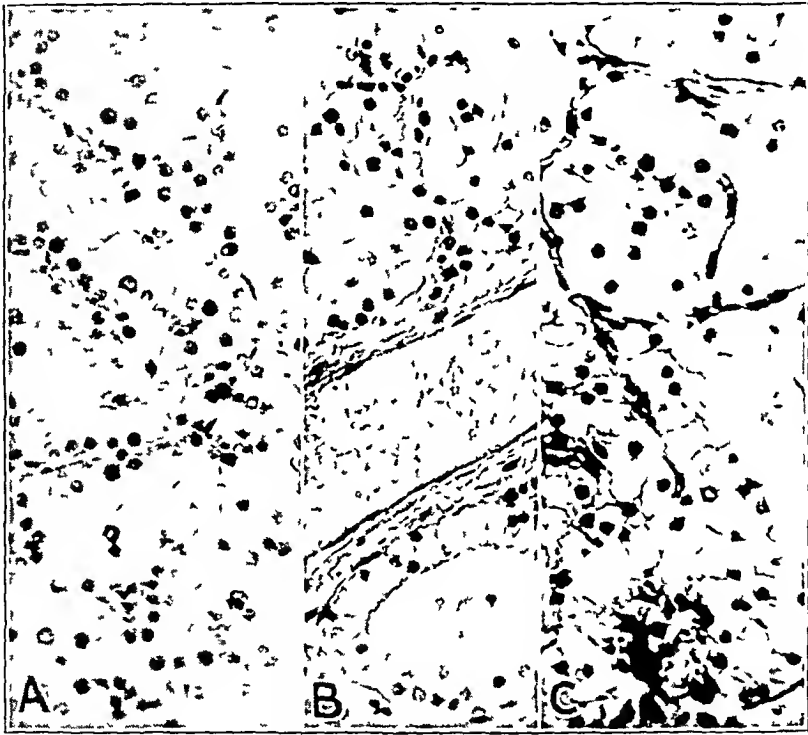


Fig 5—Photomicrographs illustrating the uniformity of structure of the parathyroid tissue in the 3 patients under consideration. A shows tissue from T F, B, tissue from J M M, and C, tissue from A P.

COMMENT

It is apparent in these 3 cases that some factor was present causing hyperplasia of all parathyroid tissue. Furthermore, hyperplasia of the parathyroids can apparently be divided into two types: that in which there is an increased need for the hormone, a compensatory hyperplasia as it were, and that in which some factor drives the parathyroid tissue to produce more hormone than is needed. Examples of the former are the hyperplasias seen in calcium privation, pregnancy, rickets, osteomalacia and possibly long-standing renal insufficiency. In these conditions, because of adverse circumstances an increased amount of hormone

is apparently needed to maintain a normal calcium level. In the 3 cases reported in this paper, however, the hyperplasia actually produced a quantity of hormone beyond that which was needed. The hyperthyroidism of exophthalmic goiter is an analogous example of a hyperplasia giving rise to more hormone than is needed.

The question arises as to what factor could be causing this hyperplasia. Hertz and Krane³ have shown that extracts of the pituitary gland contain a parathyrotropic substance which will cause hyperplasia of the parathyroid glands of recipient animals. The possibility suggests itself, therefore, that there may be hyperfunction of this factor in the pituitaries of these patients.

It consequently becomes of interest to consider what evidence there is, in these or in similar cases, of an underlying pituitary disorder. Eleven cases of multiple parathyroid enlargements, reports of which are abstracted from the literature, throw considerable light on this aspect of the question. They have been collected from a total series of 101 proved cases of hyperparathyroidism which have come to the author's attention. These 101 cases are by no means a complete series. Of course, the fact that a person has two enlarged parathyroid glands does not, per se, mean that hyperplasia and not multiple adenoma formation is present.^{3a} However, the presence of enlargement in two glands certainly suggests hyperplasia, and some, if not all, of these 11 cases certainly are analogous to our 3 cases.

CASES FROM THE LITERATURE

CASE 1 (Schmorl,⁴ Molineus⁵)—A woman, aged 48 at the time of death, had had symptoms of a pituitary tumor since she was 20. She presented the symptoms of Cushing's disease,⁶ with amenorrhea, hirsutism and obesity, plus the symptoms of osteitis fibrosa cystica. At autopsy the pituitary tumor was found to be a basophilic tumor. One parathyroid gland measured 2.3 by 1.1 by 1.2 cm., all the glands were enlarged. The kidneys were contracted. She had a colloid goiter. Histologically, the parathyroid tissue was apparently not so remarkable as in our 3 cases.

3 Hertz, S., and Krane, A. Parathyrotropic Action of the Anterior Pituitary. Histological Evidence in the Rabbit, *Endocrinology* **18** 350, 1934.

3a Since this paper went to press 4 additional patients have been studied and operated on, bringing our series to 23 cases. Case 23 was exactly similar as regards the parathyroid pathologic changes to the 3 cases here reported. Both cases 20 and 21 showed two parathyroid adenomas, making it clear that the presence of two enlarged glands does not necessarily mean that generalized hyperplasia is present. This whole subject will be discussed in detail in a paper by Castleman and Mallory to appear in the *American Journal of Pathology*.

4 Schmorl, G. *München med Wchnschr* **59** 2887, 1912.

5 Molineus. Ueber die multiplen braunen Tumoren bei Osteomalacie, *Arch f klin Chir* **101** 333, 1913.

6 Cushing, H. Further Notes on Pituitary Basophilism, *J A M A* **99**: 281 (July 23) 1932.

CASE 2 (Hoffheinz⁷) —The patient died at the age of 42 with uremia, having had typical symptoms of osteitis fibrosa cystica. Autopsy revealed, besides the skeletal disease, bilateral nephrolithiasis, calcium deposits in both kidney parenchymas, multiple adenomas of both suprarenal cortices, atrophy of both suprarenal medullas and multiple parathyroid tumors (measuring in their largest diameters 5.5, 4.5, 2 and 1.4 cm). All parathyroid tissue, including that of a fifth minute body in the thyroid, was composed mainly of *wasserhellen Zellen* and was probably not unlike that in our cases. The pituitary findings were not striking.

CASE 3 (Godel⁸) —The patient was a woman 42 years old at the time of death. Autopsy revealed that both lower parathyroid glands were markedly enlarged (5 and 10 cm in their longest diameters). The upper parathyroids were not found. The kidneys showed calcium casts. The skeleton showed typical Recklinghausen's disease. The histologic appearance of the parathyroid glands in this case, as reported, does not suggest similarity to our cases.

CASE 4 (Paul⁹) —A man, who died at the age of 56, had lost 13 Kg in the previous two years by dieting. At autopsy two parathyroid tumors, each about 6 cm in the longest diameter, were found. There was, in addition, marked enlargement of the suprarenal cortices with adenoma formation in them. Together they weighed 65 Gm (normal weight circa 12 Gm). The kidneys were enlarged and finely granular. The urine had shown albumin and hyaline casts, and the non-protein nitrogen level in the blood before death had been 100 mg per hundred cubic centimeters. The blood pressure likewise had been elevated (184 systolic and 100 diastolic). Histologically, calcium deposits were present in the liver, kidneys and blood vessel walls. The cells of the parathyroid parenchyma were described as clear, lightly staining cells with marked alveolar formation. The bones showed typical osteitis fibrosa cystica.

CASE 5 (Hellstrom¹⁰) —A woman of 44 had typical osteitis fibrosa cystica of at least five years' duration. Catamenia was still regular. She had one son, aged 19. A parathyroid gland, the size of a walnut, was removed from the left side. This was attended by only a slight fall in the elevated serum calcium level. Subsequently an equally large gland was removed from the right side. The serum calcium then returned to normal. The histologic appearance of the two glands was similar. The cells had "small nuclei rich in chromatin and a light somewhat finely granular protoplasm scarcely stainable with eosin." The tendency to alveolar and cystic formation was stressed.

CASE 6 (Bergstrand¹¹) —The patient was a 57 year old woman, the mother of three children. Her symptoms of hyperparathyroidism started simultaneously with the cessation of the menses, at the age of 55. Her blood pressure was ele-

7 Hoffheinz, S. Ueber Vergrosserungen der Epithelkörperchen bei Ostitis fibrosa und verwandten Krankheitsbildern, *Virchows Arch f path Anat* **256** 705, 1925.

8 Godel, A. Epithelkörperchentumoren bei tumorbildender Ostitis fibrosa, *Wien klin Wchnschr* **38** 247, 1925.

9 Paul, F. Ostitis fibrosa generalisata Epithelkörperchen und Nebennieren, *Beitr z path Anat u z allg Path* **87** 503, 1931.

10 Hellstrom, John. Hyperparathyroidism and Osteitis Fibrosa Generalisata, *Acta chir Scandinav* **69** 237, 1931.

11 Bergstrand, H. Ostitis fibrosa generalisata Recklinghausen mit pluriglandularer Affektion der innersekretorischen Drüsen und röntgenologisch nachweisbarem Parathyroideatumor, *Acta med Scandinav* **76** 128, 1931.

vated when first seen but diminished as time went on. Her basal metabolism was slightly elevated. Polyuria was marked. Rare granular casts without albumin were noted (cf case 16).

At autopsy there were found hyperplasia of all parathyroid glands, hyperplasia of the thyroid gland, nephrosclerosis, cholelithiasis and Recklinghausen's disease of the bones. The pituitary was histologically and grossly normal. The lower right parathyroid measured 4.5 by 2.5 by 3 cm, and the upper left, 4.5 by 2 by 0.5 cm, the remaining two glands were twice the normal size. The suprarenals weighed 10 Gm apiece. There was a leiomyoma of the uterus. The kidneys showed calcium deposits, which were most marked in the tips of the pyramids (cf granular casts, cf also Albright and Bloomberg²). All of the parathyroid tissue had the same structure. It consisted of "large, epithelial cells, rich in protoplasm." There was a tendency to form follicles. No colloid was seen. The cells contained no fat or only the least bit. There were no Welsh cells. The author called attention to the analogy with exophthalmic goiter.

CASES 7 and 8 (Hunter¹²)—Each of 2 patients reported on by Hunter had two enlarged parathyroids. The first patient, on whom autopsy was performed, was a woman of 49 with a history of osteitis fibrosa cystica for eight years at the time of death. She had had four children. Autopsy showed calculi in the pelvis of one kidney, advanced bone lesions and two parathyroid tumors (1.1 and 2.8 cm in their longest diameters). Histologically, Dr. Turnbull considered these hyperplastic rather than neoplastic and noted that the majority of the cells were "principal cells in the dropsical or ballooned state."

The other patient was a woman of 51 who had had osteitis fibrosa cystica for at least three years. She had had three children. Calculi were present in both renal pelves, and albuminuria was marked. At operation the two upper parathyroids were found to be normal and left in place, two tumors were found and removed. They measured 2 and 7.5 cm in their longest diameters. Tetany developed postoperatively. On histologic examination these glands were composed of pale oxyphil cells.

CASES 9 and 10 (Hanke¹³)—Both of the patients who came to autopsy whose cases were reported by Hanke had multiple tumors. His second case, that of a woman of 40, was more nearly analogous to the cases here under consideration. The patient died with advanced osteitis fibrosa cystica. One parathyroid was the size of a hen's egg and one the size of a walnut, and two were the size of peas. All histologically showed almost exclusively *wasserhellen Zellen* in alveolar and follicular arrangement. There was a small cortical adenoma in one suprarenal. There were changes in the pituitary of questionable significance. The kidneys were granular and contained parenchymatous calcium deposits.

The first case was that of a woman who died at the age of 33 with advanced bone disease. She had two very large parathyroid glands, but histologic examination showed these to be composed of oxyphil cells. The suprarenal glands were large (7.47 and 7.3 Gm). There were calcium deposits in the kidneys. The pituitary showed localized areas of chief cell hyperplasia.

12 Hunter, D. Hyperparathyroidism. Generalized Osteitis Fibrosa (With Observations upon the Bones, the Parathyroid Tumours, and Normal Parathyroid Glands by Herbert M. Turnbull), Brit J Surg **19** 203, 1931.

13 Hanke, H. Pathologische und theoretische Untersuchungen über Osteodystrophia fibrosa (v. Recklinghausen) und ihre Beziehung zu Epithelkörperchentumoren, Arch f klin Chir **172** 366, 1932.

CASE 11 (Abel et al¹⁴) —The patient was a woman of 58 with typical osteitis fibrosa cystica from whom two parathyroid tumors were removed, one "three times normal size" and one the "size of a walnut" Tetany developed on the sixth day following the operation

COMMENT

In addition to these 11 cases there are in this series of 101 cases 3 others with multiple tumors Two of these (one reported by Molineus,⁵ in a woman of 59, and one by Beck,¹⁵ in a woman of 41) are not considered because the evidence for uniform hyperplasia is rather scanty The other, that of a boy of 20 reported by Hubbard and Wentworth,¹⁶ was left out since the cause for the hyperplasia was probably renal disease Whereas hyperparathyroidism certainly causes renal disease, renal disease may cause hyperplasia of the parathyroids (see discussion in a previous paper¹⁷) In none of our 3 cases was there sufficient renal insufficiency to suggest this as the cause of the hyperplasia In several of the cases cited from the literature, however, this factor cannot be entirely ruled out We recently had an opportunity, furthermore, to study the glands in a patient with multiple enlarged parathyroids who died with uremia from long-standing renal disease The histologic picture in this case was not similar to that in the 3 cases here reported

If one focuses on the 11 cases abstracted from the literature and the 3 cases here reported, one finds considerable circumstantial evidence incriminating the anterior lobe of the pituitary

In the first place, it is now well established that there is an increased excretion of the gonad-stimulating hormone of the anterior lobe of the pituitary in the urine during the menopause and for years later This increased excretion was present in both of our female patients (aged 62 and 65) Hellstrom's patient was a woman of 44, Bergstrand's patient had the onset of her symptoms at the menopause, Hunter's 2 patients were 49 and 51, respectively, Hanke's second patient was a woman of 49, the patient observed by Abel and his associates was a woman of 58 Eight of the 14 patients, therefore, probably had an increased activity of this factor of the pituitary as part of the menopause On the other hand, our male patient gave a negative reaction to a test

14 Abel, A L, Thomson, G, and Hawksley, L M Generalized Osteitis Fibrosa Case Successfully Treated by Removal of Parathyroid Tumours, *Lancet* 2 525, 1933

15 Beck, A *Arch f klin Chir* 152 123, 1928

16 Hubbard, R S, and Wentworth, J A A Case of Metastatic Calcification Associated with Chronic Nephritis and Hyperplasia of the Parathyroids, *Proc Soc Exper Biol & Med* 18 307, 1921

17 Albright, F, Baird, P C, Cope, O, and Bloomberg, E Studies on the Physiology of the Parathyroid Glands IV Renal Complications of Hyperparathyroidism, *Am J M Sc* 187 49 (Jan) 1934

for this substance. We have, furthermore, evidence which shows that the parathyreotropic substance of Hertz and Kianes is not identical with the gonad-stimulating hormone from the pituitary.

The gonad-stimulating hormone of the pituitary is thought to be connected with the basophilic cells of that organ. Therefore, the case of Schmorl and Molineus, in which a basophilic adenoma was present, again suggests a relationship with this hormone, in any case with the pituitary. Cushing,⁶ of course, has emphasized the presence of osteoporosis in patients suffering from basophilic tumors of the pituitary, and has predicted parathyroid hyperplasia in such cases.

The anterior lobe of the pituitary, furthermore, exerts a marked stimulating effect on the suprarenal cortex. Of the 14 patients under consideration, 7 were examined post mortem. Of these 7, Hoffheinz' patient showed multiple cortical adenomas, Paul's patient had markedly enlarged suprarenals (65 Gm together), Bergstrand's patient had enlarged suprarenals (10 Gm each), and both of Hanke's patients had enlarged suprarenals and 1 had an adenoma of the suprarenal cortex. The suprarenals were not mentioned as being hypertrophied in Molineus' patient with typical Cushing's disease, but this is a part of that condition. There is, therefore, evidence incriminating the suprarenal cortex-stimulating factor of the anterior lobe of the pituitary in these cases as well.

There the matter must remain for the time being. It seems almost certain that such patients have an overabundance of a parathyroid-stimulating factor, it seems not unlikely that this is identical with the substance described by Hertz and Kranes. Even so, what relation such a substance bears to other pituitary factors remains for the future to determine. With the aid of Dr. Hertz, studies aimed at the isolation of a parathyroid-stimulating factor from the urine of these patients are being conducted.

The treatment of generalized hyperplasia of parathyroid tissue with hyperparathyroidism is still to be worked out. Certain facts seem apparent. Surgical intervention directed at the parathyroid glands has certain difficulties with which to contend. Complete removal of all parathyroid tissue must be avoided until a more satisfactory replacement treatment is available. A subtotal removal will be satisfactory only if something analogous to what occurs in exophthalmic goiter is found to hold for this condition. Thus, if it is learned by experience that there is a certain fixed amount of hyperplastic tissue which can be left in place—too little to regenerate and again cause hyperparathyroidism but sufficient to prevent the parathyreoprivic state—then and only then, will the condition be amenable to surgical treatment. To learn how much such a fixed amount might be, if existent at all, it will be necessary in such cases that the surgeon endeavor to see all parathyroid tissue and

to know exactly what is being removed and what is being left behind. Figure 6 has been constructed with this in view. Case 17 is especially instructive, as all of the glands were accounted for. A glance at table 3 shows that the desired end was obtained to date in this patient. It is of course too early in any of these cases to discuss the results of treatment. We merely wish to outline the problem. Roentgen irradiation may even have to be reconsidered. Although it has not been of value in this clinic in cases of parathyroid adenoma it may help in the cases of hyperplasia.

The pathologist may be of considerable help to the surgeon at the time of operation. The histologic structure in these cases is so characteristic that a frozen section from a biopsy specimen from the first gland found should make it clear whether the condition under consideration

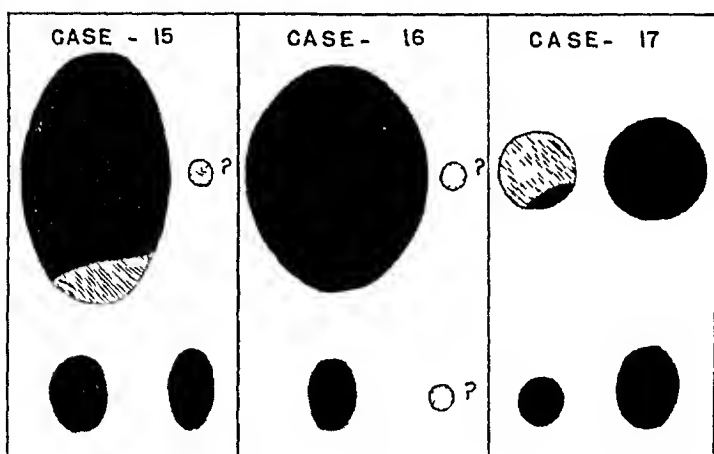


Fig 6—A schematic representation of parathyroid tissue removed (solid black), parathyroid tissue seen and left (diagonal lines) and parathyroid glands not accounted for (dots). This figure was drawn to scale but has been much reduced in size in the printing. The glands not accounted for were drawn with dimensions of 0.5 by 0.5 cm, the approximate size of a normal gland.

is present. If it is, exploration surely should be continued. If not, it does not mean that there may not be other enlarged glands, as certain cases in the literature certainly suggest the possibility of multiple adenomas, but they are much less likely to be present. In case 18 in this series an exploration difficult because of an adenomatous thyroid was discontinued when the frozen section of the parathyroid enlargement removed was interpreted as not showing hyperplasia.

We attach no significance to the fact that none of our 3 patients had bone disease. We consider this a complication of the disease, dependent on duration, degree and dietary habits, rather than a necessary feature. The metabolic findings were typical of hyperparathyroidism. The data for the urinary excretion of calcium and phosphorus were

not given, but very large amounts were excreted by patients 15 and 16, for whom these values were determined

SUMMARY

Three patients with clinical hyperparathyroidism were found at operation to have multiple parathyroid enlargements, considered to represent hyperplasia of all parathyroid tissue

The histologic structure of the glands in these patients differed markedly from that in 16 cases from the clinic in which only solitary parathyroid enlargements were present. The distinctive features were the uniformity of structure, the enormous size of the cells, the extreme clearness of the cytoplasm and the tendency to glandular formation

A distinction is made between parathyroid hyperplasia with hyperparathyroidism and compensatory hyperplasia of the parathyroid glands. An analogy between the former and exophthalmic goiter is made

Hyperplasia of the parathyroid glands with hyperparathyroidism is considered a disease entity

The surgical treatment of parathyroid hyperplasia with hyperparathyroidism brings up some interesting questions. Thus removal of two enlarged glands in one of these patients was without effect on the serum calcium and inorganic phosphorus levels. Even with removal of sufficient tissue to alter the blood chemistry satisfactorily, the condition is apt to recur. It is still undecided whether this condition can be handled by surgical means

A review of 101 cases of hyperparathyroidism revealed 17 cases, including these 3 in which there were multiple parathyroid enlargements. Several are undoubtedly similar to the ones here reported

The records of the cases of multiple parathyroid tumors have abundant circumstantial evidence in them to suggest that the pituitary gland is incriminated

The cause of the hyperplasia is probably a parathyroid-stimulating factor, possibly the one of the anterior lobe of the pituitary described by Hertz and Kianes

HYPOGLYCEMIA IN DIABETES ASSOCIATED WITH OBSTRUCTION OF THE PANCREATIC DUCT

ISOLDE T. ZECKWER, M.D.*

PHILADELPHIA

Certain recent experimental work has raised points for discussion in connection with an unusual case of hypoglycemia which seemed difficult to interpret clinically and pathologically at the time of autopsy.

In recent years it has been shown that in totally depancreatized dogs kept under proper treatment with insulin but not fed raw pancreas a condition is likely to supervene in which weakness suddenly develops and the dog shows decreased glycosuria and lower blood sugar, becomes sensitive to insulin and finally without administration of insulin dies in a state of hypoglycemia. At autopsy such an animal shows severe fatty degeneration of the liver. Fisher,¹ among other workers, described this condition incidentally in a depancreatized dog which died with a blood sugar content of only 0.013 per cent. The pathologic condition of the liver has been discussed in experiments described by Allan, Bowie, Macleod and Robinson,² who, however, did not record the blood sugar values or the response to insulin at this stage. They found a fat content of the liver as high as 35.5 per cent. Many workers had found that feeding diabetic dogs raw pancreas kept them in good condition, and that when the feeding of pancreas was discontinued they were likely to die in spite of insulin.

These isolated facts have been gathered together and their significance explained by Hershey and Soskin,³ who showed that in the absence of the external enzymes of the pancreas in the depancreatized dog hepatic injury occurred, characterized functionally by a low blood sugar and sensitiveness to insulin, with death in a state of hypoglycemia even though insulin was discontinued, anatomically by gross degeneration of the liver and microscopically by fatty changes in the hepatic cells. They found that when animals who showed the beginning of this syndrome were fed lecithin derived from egg yolk they promptly recovered, and at autopsy the liver was free from fat. The lecithin had

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1 Fisher, N. F. *Am. J. Physiol.* **67**: 634, 1923.

2 Allan, F. N., Bowie, D. J., Macleod, J. J. R., and Robinson, W. L. *Brit. J. Exper. Path.* **5**: 75, 1924.

3 Hershey, J. M., and Soskin, S. *Am. J. Physiol.* **98**: 74, 1931.

apparently restored to the liver its ability to form sugar, which was interfered with by the fatty degeneration. In 1932, Best and Hershey⁴ studied more fully this hepatic insufficiency in depancreatized dogs which were not fed raw pancreas. The stage of hepatic insufficiency can be precipitated by the feeding of fat. When fat is fed to a diabetic dog, there is a decrease in glycosuria, and the blood sugar becomes so low that the insulin dosage has to be reduced. They said

We suggest that the explanation of these results is that the fat feeding produces changes in the liver which inhibit gluconeogenesis in this organ to such an extent that the blood sugar is only slightly raised above the normal level, and very little sugar appears in the urine. These animals are apt to die very suddenly, however, and the livers are then found to be very friable and to contain amounts of saturated fatty acids. It is possible to improve "the chemistry" of the diabetic organism without improving the clinical condition.

Even when a diabetic dog appears moribund in this stage of hepatic insufficiency he can be completely restored by lecithin.

In 1933 Best, Ferguson and Hershey⁵ found that choline hydrochloride given to diabetic dogs prevented fat from accumulating in the liver even when the dogs were fed a diet high in fats but they now said "We can no longer associate, as intimately as previously seemed justified, the elimination of excess liver fat and increased production of sugar." The administration of betaine, as well as choline, prevented the deposition of fat in the liver of normal rats that were fed fat.⁶

Berg and Zucker⁷ deprived dogs of pancreatic juice by means of fistulas and by ligation of the pancreatic ducts. They described striking degenerative changes in the liver which they considered to be "practically identical with those following pancreatectomy" as described by Hershey and Soskin. They did not, however, state the blood sugar values or prove that hypoglycemia developed in their animals, but it seems probable that this hepatic dysfunction would occur in the absence of external enzymes of the pancreas, no matter in what manner the enzymes are excluded.

There is abundant evidence that hepatic damage causes hypoglycemia in nondiabetic animals. Furthermore, we know from the work of Mann and Magath⁸ that when a dog is depancreatized, resulting in

⁴ Best, C. H., and Hershey, J. M. *J. Physiol.* **75**: 49, 1932.

⁵ Best, C. H., Ferguson, A. C., and Hershey, J. M. *J. Physiol.* **79**: 94, 1933.

⁶ Best, C. H., and Huntsman, M. E. *J. Physiol.* **75**: 405, 1932.

⁷ Berg, B. N., and Zucker, T. F. *Proc. Soc. Exper. Biol. & Med.* **29**: 68, 1931.

⁸ Mann, F. C., and Magath, T. B. *Studies on the Physiology of Liver, Effect of Total Removal of Liver After Pancreatectomy on Blood Sugar Level*, *Arch. Int. Med.* **31**: 797 (June) 1923.

hyperglycemia, and the liver is removed the blood sugar falls and the dog dies in a state of hypoglycemia. These investigators say that the experiments

prove conclusively that the liver is absolutely necessary for the maintenance of the blood sugar level in the hyperglycemic animal in the same manner as in the normal animal. The increase in blood sugar following pancreatectomy is dependent on the presence of the liver. Without an adequate amount of functioning liver tissues, the increase in blood sugar following pancreatectomy could not occur.

Recent personal experience with a depancreatized dog that died of hepatic insufficiency made vivid the manifestations of this syndrome described by Hershey and Soskin and called to mind an autopsy made two years ago, in which the patient presented what seemed to be an analogous syndrome. In a restudy of this clinical case, certain points of similarity and difference were found between the clinical and the experimental findings. These comparisons were made in the hope that they might prove useful to the clinician who is applying experimental facts to the living patient and to the research worker who is seeing how far the artificial conditions produced in animals have a counterpart in the spontaneously occurring conditions in the human being.

The patient had a history of diabetes, but had been unwilling to cooperate and had received no insulin. He came to the hospital moribund and in a state of hypoglycemia. It was stated that he had been eating little for a week before admission. Intravenous administrations of dextrose promptly brought him out of coma and mental confusion, but he relapsed several times into hypoglycemic shock. Autopsy revealed that pancreatic calculi and calcification had caused almost complete atrophy of the acinar and island cells of the pancreas. This amazing atrophy, which is described later, is the closest possible clinical parallel to experimental pancreatectomy in dogs. No pancreatic juice was available to this patient. The liver showed degenerative changes microscopically. These are described later.

REPORT OF A CASE

CASE 1—History—A man, aged 53, was admitted to the University Hospital on Jan 28, 1931, in the service of Dr Stengel. He died on Feb 2. The chief complaint was weakness. About two years previously an enormous appetite, polydipsia and polyuria had developed. During the year preceding admission he suffered from weakness and lost 30 pounds (13.6 Kg). Six months previous to admission he was unable to continue work. He was told at this time that he had severe diabetes. He was unwilling to be hospitalized or to follow a diet. He never received insulin. He had had constipation for many years. Three months previous to admission a cough with expectoration and shortness of breath developed. During the week before admission he lost his appetite, had chills and profuse sweats and was extremely weak.

Examination on admission revealed physical signs of bilateral pulmonary tuberculosis. The patient appeared almost moribund. At times he was irrational and at times comatose. Emaciation was extreme. Sweating was profuse, and the body was cold. The urine was free from sugar, and the blood sugar only 0.052 per cent. Dextrose was given intravenously, and after about half of the solution had been introduced, the patient became conscious and carried on a rational conversation. Although he had not eaten much for a week or more before admission, there was no evidence of acidosis due to starvation.

The next day the blood sugar was 0.089 per cent. The patient's mental state improved, and he took fluids well. During the evening he became irrational, he wanted to get out of bed and pulled his face into strange contortions. The attack lasted fifteen minutes, after which he became quiet and rational. The feces showed the presence of fat in large amounts.

On the third day, the patient ate a diet high in calories. On the fourth day, the blood sugar was 0.263 per cent. On the fifth day, he became unconscious. The blood sugar was 0.100 per cent. Intravenous injections of dextrose were given, following which the patient became conscious and rational. On the sixth day he suddenly became unconscious again and could not be revived by dextrose administered intravenously, but died. The blood sugar on that day was 0.143 per cent.

Relevant Observations Made at Autopsy—Postmortem examination was made by Dr. G. H. Klinck, Jr. one and one-half hours after death.

The gross anatomic diagnoses were emaciation, bilateral pulmonary tuberculosis with cavitation, congestion of the liver and atrophy of the pancreas with multiple calculi in the duct.

Histologic diagnoses of pulmonary tuberculosis with caseation and cavitation, parenchymatous degeneration and congestion of the liver, atrophy of the pancreas and remnants of islet and acinous tissue were made.

Pancreas No pancreatic tissue could be found. A tract of rather loose fibers containing the splenic artery and vein was found, and the pancreatic duct extended from the duodenum to the spleen. In this mass numerous hard bodies averaging from 3 to 15 mm. could be palpated, most of them were oblong. The pancreatic duct was fused and contained large numbers of calculi. The duct was considerably dilated and in some places was 16 mm. in circumference. The walls of the duct were thick. Some of the calculi were spherical, and others oblong, all of them were rough and surrounded by a thick, milky material.

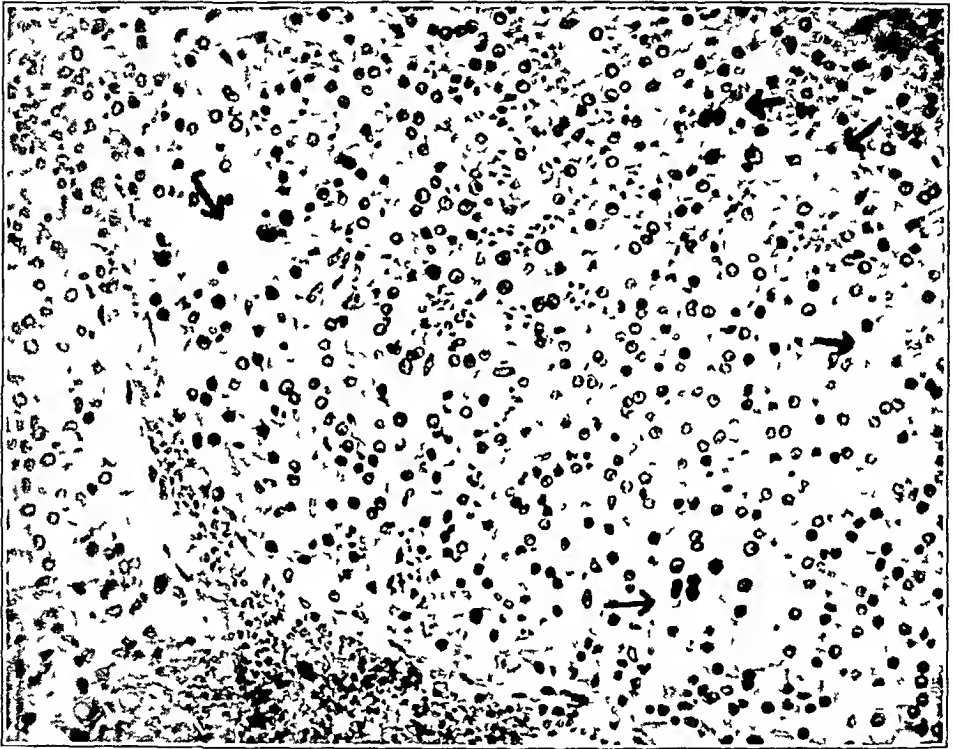
Three sections which had been taken from the usual site of the pancreas and which contained calcareous deposits were studied. In two of the sections there were extremely small bits of pancreatic tissue consisting of small acini composed of typical acinar cells, but no islet tissue was found. The sections had been decalcified, and the decalcified portions showed their characteristic irregular pale bluish-pink structures. One section included a section of a large duct which was lined by what appeared to be transitional epithelium. Several large vessels were included in this section, but they showed nothing of interest.

Further examination of the pancreas revealed small round areas composed of epithelial cells. The arrangement of the cells was more like that of the cells of islet tissue than that of acinous tissue. In most instances the cells were comparatively small, and their nuclei pyknotic. Here and there a few cells showed vesicular nuclei resembling the structure of normal islet cells. In addition, a number of the islands of epithelial tissue showed areas of hyalinization of the type frequently seen in pancreatic islet tissue. The size of the bodies was approxi-

mately that of normal islands of Langerhans. They were believed to be islands showing degeneration of epithelial cells characterized by pyknosis and hyalinization.

Liver. The liver weighed 1,100 Gm and measured 26 by 20 by 7 cm. It was extremely small in size and weight, but when compared to the weight of the subject (40 Kg) its small size is not out of proportion. It was free from adhesions and firm and dark. On section it cut with increased resistance, and a small amount of blood escaped. The parenchyma was homogeneous, and no structures of the lobules could be made out.

Microscopic sections of the liver were restudied. The sinusoids showed an excess of red cells uniformly distributed throughout the lobule. There was no distention of the central veins. The hepatic cells showed small vacuoles, but fatty



Photomicrograph of the liver. A few small areas are seen where nuclei have disappeared, and in close relation to these areas regeneration is indicated by cells with closely placed young nuclei.

changes were not prominent. The nuclear changes were the most conspicuous (figure). In small areas nuclei were absent. Many nuclei were large and stained poorly, giving the appearance of lysis. Others were pyknotic. Many cells were newly regenerated, as evidenced by closely placed hyperchromatic nuclei and cytoplasm more eosinophilic than those of other cells, and these areas of regeneration directly bordered on areas where nuclei had disappeared. There were no areas of frank necrosis.

COMMENT

At the time of autopsy, the absence of functioning pancreatic tissue explained the patient's history of diabetes, but it was difficult to reconcile this absence with the obvious hypoglycemia before he died. The

comment of the pathologist at the time was "The low blood sugar found just before death, in the presence of extreme diabetes, is explained by a total pancreatic insufficiency as a result of which glyco-genic food materials passed through the gastro-intestinal tract unchanged and hence in an unabsorbed state. Thus the subject may be said to have died of pancreatic insufficiency rather than of diabetes."

Experimentally, in the absence of pancreatic juice, there is an adequate absorption of fat, protein and carbohydrate if plenty of food is ingested. The factor of undernutrition was important in this case. Not only did the patient have extensive tuberculosis with cavitation, but he was said to have eaten little for a time before admission, and of what he ate a certain portion was not digested in the absence of pancreatic juice. Joslin⁹ said that in the Allen undernutrition era there were instances of hypoglycemia in diabetic patients, and that the first deaths were startling and at the time unexplained. He discussed the cases of 7 diabetic patients (4 of whom were his own) who died in a state of hypoglycemia which he ascribed to undernutrition.

It has been the experience of many that when tuberculosis develops in a diabetic patient the diabetes may seem to improve or entirely disappear as indicated by the blood sugar level. However, I have found no mention of a case in which true hypoglycemia developed when insulin was not given. Joslin said that presumably the diabetes improves because the burden on the pancreas has been decreased by undernutrition, but with this explanation he stated, "I am not wholly satisfied, because it seems illogical to attain strength through weakness." May it not be that fatty changes in the liver, which so often result from pulmonary tuberculosis, are hindering glycogenesis, and that the apparent improvement in the "chemistry" is not really an improvement? If this is true it throws new light on Joslin's comment in relation to tuberculosis.

Many diabetics are cachectic at the time of death, but this condition has by no means modified the disease. On the other hand, when cachexia due to a cause other than diabetes occurs in a diabetic, it may be responsible for improvement in the diabetes.

The question then is: Did the hypoglycemia in this patient depend on undernutrition or on deprivation of pancreatic enzymes? Hypoglycemia due solely to fasting has not been demonstrated in the experimental animal so far as I am aware. On the other hand, in the case reported here it is important to emphasize that the hepatic degeneration was not so severe as that described in the experimental animals deprived

⁹ Joslin, E. P. *The Treatment of Diabetes Mellitus*, ed. 4, Philadelphia, Lea & Febiger, 1928.

of pancreas The actual amount of fat present was negligible, it was much less than appears in the liver of patients showing no hepatic insufficiency However, the cells showed diffuse degeneration, and extensive regeneration of hepatic cells was evident, which implied that considerable injury to the liver had occurred It is known how rapidly hepatic cells regenerate After extirpating as much as three fourths of the liver of dogs, Fishback¹⁰ found regeneration up to at least four fifths of the original weight in two weeks, and Whipple and Sperry¹¹ found that after severe chloroform poisoning in dogs, involving from one third to three fifths of each hepatic lobule, repair was almost complete in eleven days and quite complete in from two to three weeks May not several days of intravenous injections of dextrose and feeding have been responsible for the evident regeneration in this patient?

Joslin regards the association of diabetes with pancreatic calculi as rare He discussed a case which has a striking similarity to that reported in this paper A patient had a blood sugar content of 0.400 per cent Four years later, after many irregularities in diet and medication with insulin, the patient died in a state of hypoglycemia with a blood sugar content of 0.013 per cent At autopsy the pancreatic duct was obstructed by about one hundred calculi In a review of 2,800 autopsies at the Pennsylvania Hospital, Dillon¹² found only 2 cases of pancreatic calculi, in 1 of which there was glycosuria The patient, dying of tuberculosis, had extreme atrophy of the pancreas due to obstruction of the duct by numerous calculi The organ weighed only 5 Gm Only a few lobules of fibrosed acinar tissue remained The statement was made "The impression was that as a secreting organ the gland must have been almost functionless" From the data given there is no evidence that the patient died in a state of hypoglycemia On the contrary, it is stated that the tolerance for carbohydrate was low Since all depancreatized dogs do not show hepatic insufficiency, probably one should not expect every case of obstruction of the duct in patients to result in a state of hypoglycemia

In trying to locate other cases of pancreatic calculi in which autopsy was performed in this department (this includes all of the autopsies at the University Hospital and about two thirds of the autopsies at the Philadelphia General Hospital), it was found that during the years from 1917 to 1932, inclusive, the diagnosis of pancreatic calculi had been indexed only 5 times in a series of about 10,300 autopsies Examination of the clinical histories of the 5 cases showed that the only one asso-

10 Fishback, F. C. Morphologic Study of Regeneration of Liver After Partial Removal, *Arch Path* 7:955 (June) 1929

11 Whipple, G. H., and Sperry, J. A. *Bull Johns Hopkins Hosp* 20:278, 1909

12 Dillon, E. S. *Bull Amer Clin Lab, Pennsylvania Hosp*, no. 8, 1924, p. 35

ciated with diabetes was the case discussed here. The chief points in the other 4 cases are as follows:

CASE 2—A woman, aged 36, died of pulmonary tuberculosis. There was no record of the blood sugar. Glycosuria was not present. At autopsy the pancreas showed a number of small calculi in the duct, but there was apparently not much atrophy of the parenchyma. The liver showed parenchymatous degeneration and weighed only 430 Gm.

CASE 3—A man, aged 35, died of lobar pneumonia. There was no glycosuria. There was no record of the blood sugar. At autopsy the pancreas was embedded in dense adhesions. A probe could not be introduced into the pancreatic duct. Several small calculi were found in the duct. There was apparently no marked atrophy of the parenchyma.

CASE 4—A woman, aged 87, whose mental condition was ascribed to senile dementia, was unable to answer questions. No history could be taken. Glycosuria was not present. The blood sugar was 93 mg seventeen days before death. She died from no concrete cause except senility and chronic myocarditis. At autopsy, likewise, no satisfactory pathologic basis for death was found. The pancreas showed an almost complete atrophy of the pancreatic tissue, with replacement by fatty and fibrous tissue. The body of the pancreas contained two cysts, one the size of an orange and the other much smaller, which on section allowed a skim-milk, whitish fluid to escape; in the larger cyst, a small white concretion the size of a pea was found. The liver weighed 1,020 Gm, and showed mild cirrhosis, passive congestion and fatty degeneration. This case is the only one that has any resemblance to the one with which this paper is chiefly concerned. It raises the question whether, if a blood sugar determination had been made soon before death, it might not have shown a low value.

CASE 5—A man, aged 71, who had digestive disorders of long standing and advanced carcinoma of the esophagus, had eaten little before admission. The blood sugar on that day and twenty-six days before death was 124 mg. At autopsy the pancreatic duct contained several calculi, back of which the ducts were greatly dilated and filled with a white fluid. The pancreas was reduced in size, but apparently the ducts had not been obstructed long enough to cause profound atrophy of the parenchyma. The liver weighed 1,830 Gm and showed passive congestion and fatty changes grossly and microscopically.

SUMMARY

1. A patient with a history of diabetes but no medication with insulin manifested hypoglycemia. At autopsy, calculi obstructed the pancreatic duct, with resultant extraordinary atrophy of the acini and islands, the liver showed degenerative changes, and there was pulmonary tuberculosis.

2. The clinical condition paralleled experimental pancreatectomy in the dog, in which it has been shown that hepatic insufficiency results from deprivation of the external secretions of the pancreas.

3. Points of similarity between the clinical case and the experimental animal were (1) the development of hypoglycemia after the hyperglycemic period and (2) hepatic degeneration. The latter, however, was

of a minor degree and of a different gross and histologic character from that seen in dogs

4 The factor of undernutrition must be considered in the production of the hypoglycemia in this case, but has less experimental basis than the effect of loss of external pancreatic secretions

5 In 10,300 autopsies performed in this department, only 4 other instances of pancreatic calculi could be found, none of which was associated with diabetes

6 It is suggested that when the liver is damaged through loss of the external secretions of the pancreas, especially if the condition is aggravated by undernutrition and tuberculosis, hypoglycemia may result in diabetes even in the absence of treatment with insulin

INTERATRIAL SEPTAL DEFECT

H ROESLER, M D

PHILADELPHIA

The interatrial septal defect is an anatomically well known entity Louis (1826), Ecker (1839) and Cruveilhier (1852) stated the characteristic anatomic findings in the heart in the presence of a large interatrial communication the enormous increase in the volume of the heart, which is due to dilatation and hypertrophy of the right side, the marked dilatation of the pulmonary artery and its branches, and the relative smallness of the left ventricle Rokitsky's classic monograph on septal defects (1875) gives many examples of this malformation as well as embryologic explanations Ecker, a pupil of Rokitsky, also attempted to correlate the anatomic picture with the clinical picture Of the modern clinical contributions there may be mentioned especially the articles by Hoefler, Lutembacher, Muller, Assmann, Abbott and Weiss and Dressler and Roesler¹ An extensive clinical study with a complete review of the literature, however, does not exist

The detailed anatomic study of a given case permits its classification from an embryologic point of view but has apparently not much significance for the clinicofunctional conception of this entity, and the recent classification of Costa, arranged in a more distinct form, is given here only for the sake of information (table 1)

MATERIAL

Sixty-two cases (including the case reported here) form the basis for the first part of the study, in each instance a clinical as well as anatomic description was available The cases were tabulated, but only the condensed results of the tabulation are given here It is obvious that the value of the statistical approach is limited, considering that the descriptions of fifty-six different authors over a period of one hundred years had to be used The case numbers given in parenthesis correspond to those in the appendix

For certain reasons there have been excluded from this study cases of small defects measuring less than about 1 cm in diameter, cases of slits or valvelike openings in the septum (functionally separating the atria) and cases of complete absence of the septum (cor triloculare biventriculosum)

It is well known that several congenital malformations may occur in the same heart Cases which showed combinations with a patent ductus arteriosus, pulmonary stenosis, interventricular septal defect or a higher grade of coarctation of

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1 After this article was completed, the valuable contribution of McGinn and White appeared (Am Heart J 9 1, 1933)

the aorta were omitted. Other cardiovascular malformations were present in fifteen of the sixty-two cases: coarctation of the aorta of slight degree (cases 16, 36, 37 and 42), four leaflets of the aortic valve (case 23), fenestration of the aortic valves (cases 5 and 15), two openings of a coronary artery (case 55), an abnormal thebesian valve (case 23), abnormalities of the veins of the heart (cases 10, 16 and 23), cleavage of the aortic cusp of the mitral valve (cases 15, 27 and 34) and abnormality in the number or in the development of the leaflets of the tricuspid valve (cases 18 and 43) and of those of the mitral valve (case 3).

REPORT OF A CASE

Elizabeth V., aged 14 years, was well until the age of 7, at which time cardiac decompensation with edema and enlargement of the liver developed. The main clinical findings at this time were marked underdevelopment, visible pulsations of the veins of the neck, a precordial bulge and slight systolic precordial retraction. The apex beat was in the sixth intercostal space 10.5 cm. to the left of the median

TABLE 1—*Classification of Costa*

	Form	Explanation
I	Complete absence of interatrial septum	Persistence of the primitive common atrial cavity, abortive form of the septum intermedium and septum superius
II	Complete absence of the inferior portion of the interatrial septum, the defect located near the radix of the interventricular septum	Persistence of the foramen primum with agenesis of the septum intermedium
III	A gaplike status of the inferior portion of the interatrial septum not reaching down to the radix of the interventricular septum	Incomplete union between the septum superius and septum intermedium
IV	Single or multiple defects of the central and posterior portion of the interatrial septum	Agenesis of the septum secundum, persistence of the foramen secundum or of multiple equivalent foramina

line. In the third intercostal space the border of the heart was 5 cm. to the left of the median line. Systolic and diastolic thrills were felt over the apex, accompanied by systolic and diastolic murmurs. The heart rate was 108, and the rhythm regular. The pulmonic second sound was accentuated. The blood pressure was 100 systolic and 68 diastolic. The temperature vacillated up to 100 F., the respiratory rate varied from 30 to 40. The red cell count varied from 3,850,000 to 4,520,000, the hemoglobin content was 75 per cent, and the white cell count varied from 11,000 to 15,000.

The electrocardiogram (fig. 1) showed regular sinus rhythm and a high P₂. There was no pronounced axis deviation. T₁ was slightly positive, T₂ and T₃ were iso-electric. A deep Q₃ was present.

The clinical diagnosis was active rheumatic disease of the heart, mitral stenosis and regurgitation and an adherent pericardium.

The patient improved under therapy but exhibited marked shortness of breath after exertion and was often so weak that she had to remain in bed.

She was repeatedly seen from Feb. 23 to April 23, 1933 (fig. 2). The findings were marked underdevelopment, pronounced pallor and cyanosis of slight degree. There was no clubbing of the fingers, but the nails showed an increased curvature. Dyspnea and orthopnea were present. The veins of the neck were congested and

showed systolic pulsations. A precordial bulge was present. The liver was markedly enlarged and showed expansile systolic pulsations. The outermost cardiac action was seen and felt in the seventh left intercostal space in the posterior axillary line as a systolic heave of marked amplitude. During systole, retraction was noted in the third, fourth and fifth intercostal spaces. Pulsations of the heart were felt 3.5 cm below the epigastric notch, and sometimes a systolic thrill was felt over the precordium. At the apex and precordium there was a loud, harsh systolic murmur with a high-pitched blow. A rumbling systolic murmur was heard in the epigastrium. No diastolic murmur was heard at the base. The pulmonic second sound was accentuated. Along the insertion of the diaphragm inspiratory retraction of the intercostal spaces was noted. The heart rate was irregular, vary-

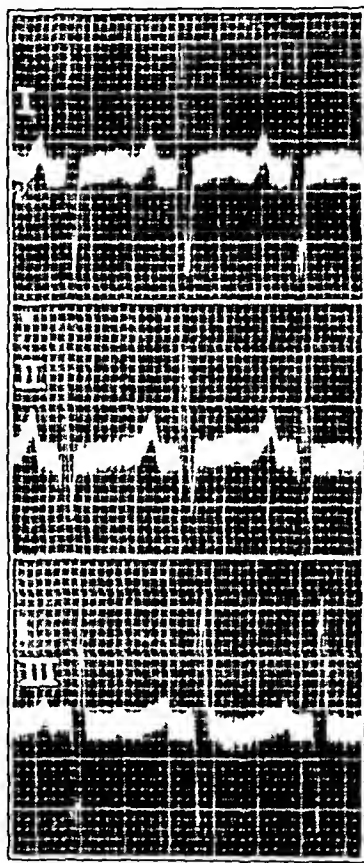


Fig 1—An electrocardiogram taken on Sept 30, 1925

ing from 80 to 120. There was poor filling of the peripheral arteries. The blood pressure was 115 systolic and 85 diastolic. The red blood cells numbered 4,160,000, hemoglobin amounted to 12 Gm per hundred cubic centimeters.

The electrocardiogram (fig 3) showed auricular fibrillation with slight axis deviation to the right, slurring of the QRS deflection in leads I and II and notching in lead III. There was a deep Q wave in lead III. The T wave was almost iso-electric in lead I and normal in leads II and III.

Roentgen examination (figs 4 and 5) showed that the heart was markedly enlarged, with a transverse diameter of 18.7 cm, an oblique diameter of 18.8 cm and an internal chest diameter of 21.6 cm. This enlargement was obviously due to an increase in the size of the right cardiac chambers. At the left side the conus arteriosus bulged upward and toward the left. The aortic arch was visible in neither the ventral nor the oblique position. There were enlargement of the

superior vena cava and encroachment by the left atrium on the posterior mediastinum, which displaced the esophagus backward and to the right. Within the pulmonary fields, the branches of the arteries were seen to be prominent and moderately enlarged, but there was no evidence of actual congestive pulmonary failure. The pulsations of all of the borders were small, they were practically absent at the right side. The diaphragm had a low position.

In the terminal stage marked cyanosis developed.

From a diagnostic point of view, a lesion of the mitral and tricuspid valves seemed most likely. Adhesive pericarditis was considered as a possibility, but

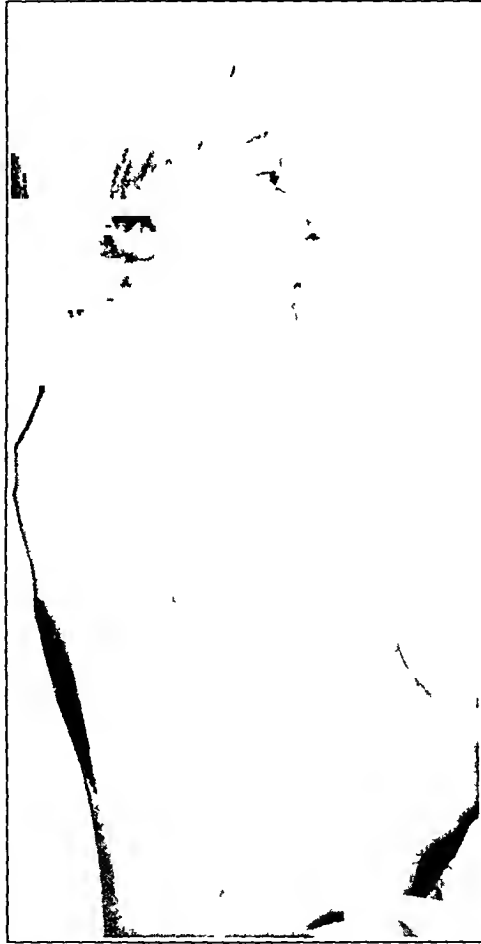


Fig 2—Photograph taken March 6, 1933. The precordial bulge and the prominence of the upper part of the abdomen caused by the enlarged liver can be seen.

evidence was not sufficient to prove this diagnosis, especially since systolic retractions are commonly seen when the right ventricle forms a considerable portion of the left contour of the heart. Congenital disease of the heart was considered because of (1) the marked physical underdevelopment, (2) the roentgen evidence of hypoplasia of the aorta and the tremendous enlargement of the pulmonary conus, and (3) the enlargement of the interpulmonary branches of the pulmonary artery, which was of a type that did not correspond to that seen in congestion. In brief, the diagnosis at the time of the patient's death was congenital heart disease with a superimposed lesion of the mitral and tricuspid valves due to rheumatic heart

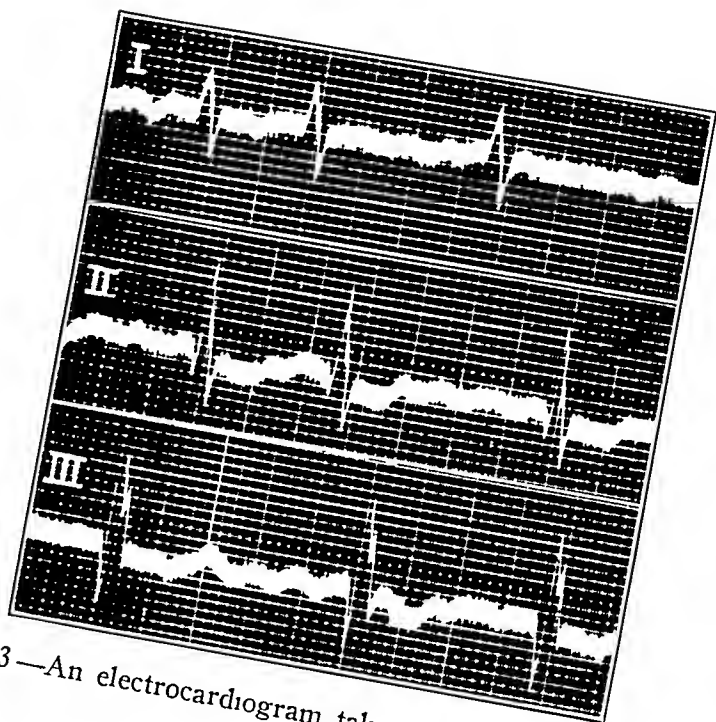


Fig 3—An electrocardiogram taken on March 20, 1933



Fig 4—Roentgenogram of the chest taken at a distance of 7 feet (213 cm)
 The globular enlargement of the heart, the enormous prominence of the conus
 arteriosus, the widening of the intrapulmonary vessels and the low position of the
 diaphragm can be distinguished Barium sulphate in the esophagus reveals its
 displacement to the right Compare figure 4 with figure 6

disease As to the underlying congenital disease of the heart, the possibility of the presence of an interatrial septal defect was mentioned

Autopsy was performed by Dr Louis A Soloff His report of April 22, which I have shortened to the main observations, is as follows The subject was a pale, emaciated, poorly developed white girl, corresponding in development to a girl of about 11 years of age The height was 139 cm The chest was somewhat asymmetrical, the left half bulging forward and to the left There was a moderate bilateral hydrothorax, hydropertoneum, edema of the lower extremities and congestion in all of the organs

The heart was markedly enlarged, fixed in formaldehyde, it weighed 800 Gm The anteroposterior diameter of the chest was 19 cm, and the heart with its



Fig 5—Roentgenogram of the chest taken at a distance of 7 feet, in the right anterior oblique position The enormous increase in the depth of the heart is seen The ventral portion of the cardiac shadow is composed of the right ventricle and the dorsal portion of the left atrium, which displaces the barium-filled esophagus

pericardial sac occupied fully 17 cm of this Except for a few fine violin-like strings of fibrous tissue, extending from the pericardium to the right hilar region of the lung, there was no evidence of extrapericardial adhesions The pericardium was smooth and thin The parietal epicardium was glistening and smooth The heart floated in about 100 cc of fluid similar to that present in the abdominal and pleural cavities Virtually the entire anterior aspect of the heart was occupied by a tremendously dilated right auricle and ventricle (fig 6) A small strip of the left ventricle was visible, approximately 0.5 cm in width at the apical region The

right auricle measured 6 cm in its anteroposterior diameter, the right ventricle was 10.5 cm wide. The conus arteriosus was tremendously enlarged upward and to the left and completely obscured the pulmonary artery, which extended directly backward toward the vertebra. The aorta was almost completely hidden from view and was apparently hypoplastic. There were many small petechiae running parallel and above the auriculoventricular junction. The visceral epicardium was smooth, glistening and transparent. There was a moderate amount of adipose tissue encircling the heart at the auriculoventricular junction. The myocardium was moderately firm and light brown. The left ventricle in its greatest diameters



Fig. 6—Photograph with the viscera in situ (April 24, 1933). Note the enormous size of the right atrium and the right ventricle. The left ventricle is barely visible. The aorta is small and the pulmonary artery large. The conus arteriosus is huge. The diaphragm is low in position.

was 10 by 7.5 by 4 cm. The endocardium here was smooth and glistening. There was a muscular band extending transversely across the left ventricle approximately at the junction of the lower and the middle thirds, attached to the trabeculae carneae, and in its center giving off a branch anteriorly to the ventricular septum. The aortic orifice was 5.4 cm in circumference. The cusps were thin and glistening but not translucent. Each one averaged 1.5 cm in width. The left ventricular wall averaged 1.3 cm in diameter. The left auricle in its greatest diameters was 7 by 4 by 6 cm. The posterior mitral leaflet was considerably shortened, thickened

and rolled, so that it extended at the greatest part only 0.4 cm from its attached margin to its free margin. Along the free edge on its auricular surface were many thin, firm, elevated verrucous vegetations. These were firmly attached to the leaflet. There was one huge chorda tendineae to which the entire valve was attached. The anterior mitral leaflet was slightly thickened, opaque and fibrous, and it measured 3.8 cm from its attached margin to its free margin. The circumference of the mitral valve was 10.5 cm. The auricular endocardium was smooth and glistening but slightly thickened. There was a large defect in the auricular septum which was seen more clearly from the right side and which will be described with the right auricle.

The right ventricle in its greatest diameters was 10.5 by 4.5 by 8 cm. The endocardium was glistening and thin and raised by numerous flat trabeculae carneae. The tricuspid orifice was 1.7 cm. The leaflets were opaque and slightly



Fig 7—Photograph of the opened heart as seen from the right side. Note the interatrial septal defect and the enlargement of the right atrium and the right ventricle.

thickened. There was an occasional rolled thickening of the free margins of the leaflets. The right ventricular wall averaged 1.2 cm in thickness. The right auricle in its greatest diameters was 11.5 by 6 by 6.5 cm. The endocardium was smooth and glistening but opaque. The fossa ovalis was 5.5 cm in diameter. There was a large opening in the upper anterior portion of the fossa which averaged 1.3 by 4 cm (fig 7). The auricular septum here was extremely thin, averaging from 1 to 2 mm. There were many small fenestrations of the fossa ovalis beneath and posterior to the large opening. These varied in diameter from that of a pinhead to 0.4 cm. The orifice of the coronary sinus below the fossa ovalis was enlarged, being 1.3 cm in diameter, and there were several fairly large fenestrations of the auricular septum anterior to this which led directly into the coronary sinus. The right auricular wall averaged 0.4 cm, and the left auricular wall 0.3



Fig 8—Photograph of the opened heart as seen from the left side. Note the absence of enlargement of the left ventricle, the thickening of the mitral valves and the narrowness of the aorta. Compare the size of the aorta and the aortic valves with the size of the pulmonary artery and its valves as seen to the left and from above.

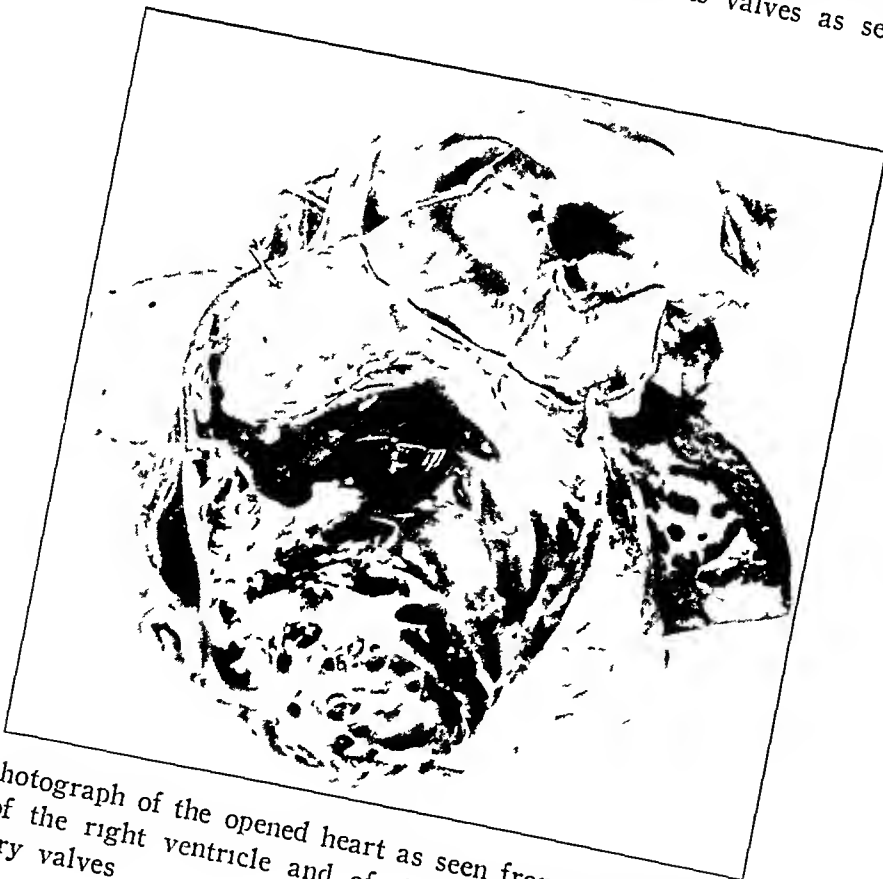


Fig 9—Photograph of the opened heart as seen from the right side. Note the enlargement of the right ventricle and of the pulmonary artery as well as the large pulmonary valves.

cm in thickness. The orifices of the coronary arteries were patent and apparently normal. The arteries, however, were not dissected.

Microscopic examination showed acute degeneration of the myocardium and fragmentation, fatty infiltration, fibrosis and thickening of the left auricular endocardium.

The aorta was lined throughout with smooth, glistening intima. At its origin, it was 5.4 cm in circumference, 2 cm above the valve it was 5 cm in circumference, and 10 cm above the valve, 3.8 cm in circumference (fig. 8). The pulmonary artery 2 cm above its origin was 9 cm in circumference (fig. 9). The left pulmonary artery was 1.8 cm in diameter, and the right pulmonary artery, 1.7 cm in diameter. The lungs resembled each other and were crowded upward and backward so that they occupied virtually only the upper third of the thoracic cage. They were covered with thin pleura. The microscopic examination indicated early bronchopneumonia and occasional mild sclerosis of the medium-sized vessels.

ANALYSIS OF CASES

Age—In the sixty-two cases forming the basis of this study the average age of the patients was 36 years, the youngest subject was 11 months and the oldest

TABLE 2—*Classification of Subjects into Age Groups*

Age Group	Number of Cases	Per Cent
0-10	5	8.0
11-20	8	12.9
21-30	15	24.2
31-40	9	14.5
41-50	10	16.1
51-60	10	16.1
61-70	3	4.8
71-75	2	3.3

75 years. Death took place within the age groups indicated in table 2. In the great majority of the cases death took place with symptoms of cardiac failure. In twelve cases death occurred from other causes than cardiac disease. These were ruptured appendix (case 27), extensive tuberculosis of the lungs (cases 11 and 29), operation (case 56), abscess of the lung (case 14), meningitis (cases 21 and 45), leukemia (case 26), renal disease (cases 36 and 39), coronary thrombosis (case 47) and septicemia (case 18). The average age of these twelve patients was 32½ years.

Sex—There were twenty-three cases in males (38.3 per cent), thirty-seven cases in females (61.7 per cent) and no statement as to sex in the remaining two cases.

Habitus—Physical underdevelopment, including infantilism and dwarfism, was noted in twenty-one cases (1, 5, 6, 10, 14, 23, 24, 25, 31, 33, 35, 40, 41, 42, 48, 49, 52, 55, 59, 61 and 62). Normal physical development was recorded in seven cases (4, 12, 18, 22, 27, 39 and 60). As to the former group, the weight for two children was 4,250 Gm at the age of 11 months (case 25) and 3,600 Gm at the age of 2 years (case 35).

Pathologic Anatomy of the Heart and Great Vessels—The defect was usually a single one, more rarely multiple, when it was multiple, the most common number of openings was two (cases 3, 6, 16, 20, 23, 32, 36, 45, 48, 58 and 60). The defects

were usually round, but were sometimes oval, with a diameter of from 1 to 5.5 cm. Multiple openings the size of a pinhole occurred in addition to the main defect.

It seems necessary to describe first the frequent occurrence of structural lesions other than congenital, namely, valvular deformities, and to follow with general considerations of the size and weight of the hearts. These valvular lesions were of the chronic fibrotic type, and it is not possible to judge their duration. A definite lesion of the mitral valve was described in thirty cases (cases 2, 4, 5, 6, 12, 15, 17, 18, 19, 21, 22, 24, 28, 30, 31, 32, 33, 34, 37, 38, 42, 48, 49, 50, 51, 52, 55, 56, 58 and 62), of which six presented the buttonhole type (cases 2, 17, 37, 38, 49 and 51), in others only mitral regurgitation was mentioned (cases 5, 15, 19, 21, 34, 50 and 52). In two of these cases cleavage of the aortic cusp of the mitral valve was mentioned (cases 15 and 34). Tricuspid regurgitation occurred in six of them, and aortic regurgitation and/or stenosis in three. In addition there are nine other cases in which thickening or a lesion of the mitral valve was described (cases 7, 11, 14, 26, 35, 41, 53, 57 and 59). Association with a lesion of the tricuspid valves was found twice, with thickening of the pulmonary valve, three times, with pulmonary regurgitation and thickening of the tricuspid valves, once. A lesion of the mitral valve was probably present in two other cases (16 and 61), in one of which there were also aortic regurgitation and probably stenosis. This brings the number of definite or most probable lesions of the mitral valve to forty-one (66.1 per cent). A lesion of the tricuspid valve without other pathologic valvular involvement was mentioned only once (case 54). There was no case with an isolated, definite aortic regurgitation and/or stenosis, aortic stenosis being present probably once (case 29). In four cases of definite lesions of the aortic valves (cases 12, 16, 17 and 58) a definite or probable lesion of the mitral valve was present three times. In three other cases thickening and slight adhesions of the aortic valves were reported (cases 5, 6 and 13), in two of which there were also changes in the mitral valves. There were two cases with pulmonary regurgitation (cases 7 and 40), in one of which there was also thickening of the mitral and aortic valves, in six other cases thickening of the pulmonary valves was reported (cases 8, 11, 12, 21, 35 and 41), in five of which there were changes in the mitral valves. Thus it can be stated that of sixty-two cases with interatrial septal defect, forty-eight (77.4 per cent) had chronic valvular lesions of different degree, affecting one or several of the valves. In addition, functional tricuspid regurgitation was mentioned ten times, and pulmonary regurgitation once. Normal valves were described in five instances (cases 9, 20, 36, 39 and 46), while the status of the valves was not mentioned in nine instances (cases 1, 10, 23, 25, 29, 43, 44, 47 and 60).

Practically all of the hearts were large or very large. The enlargement affected only, or predominantly, the right chambers. Hypertrophy was noted as a rule, but the dilatation was predominant—almost in disproportion. A few figures will illustrate the size. A heart three times larger than normal (case 4), a cardiac circumference of 47 cm (case 34) and one of 35 cm (case 55), a content of the atria and the right ventricle of 1 liter, a width of the heart of 18.7 cm and a height of 13.5 cm (case 1), a width of 17 cm and a height of 15 cm (case 49), a width of 15 cm, a length of 16 cm and a depth of 13 cm (case 40), a depth of 17 cm (case 62), a right ventricle composing three fourths of the heart (case 26), a right atrium the size of a fist (case 24), a right atrium with a width of 12.5 cm and a height of 8.7 cm (case 1), a right ventricle 10.5 by 4.5 by 8 cm and a right atrium 11.5 by 6 by 6.5 cm (in a child [case 62]), and a right auricle as large as a right atrium of normal size (case 52). The shape of the

heart was usually described as globular (cases 39, 40, 57, 58 and 62) If one leaves out all of the cases with lesions of the mitral, pulmonary and tricuspid valves and also all of the cases in which a description of the valves was lacking, there remain five cases (cases 9, 13, 20, 36 and 46) All of them showed hypertrophy of the right ventricle and atrium, with the exception of one case (case 36) in which there was no dilatation of the right ventricle Only once (case 22) was there no cardiac enlargement If one omits all of the cases in which there were left-sided valvular lesions or nephritis and all those in which a description of the valves was lacking, there remain seven cases (8, 9, 20, 36, 40, 46 and 54) In three of them the size of the left side was not given In the remainder (cases 9, 36, 44 and 54) a moderate enlargement of the left ventricle was mentioned three times In one case, there was actual narrowness of the left ventricle with slight thickening of the wall (case 54) The left atrium was moderately enlarged in two cases, and markedly enlarged in one (case 40)

Seen *in situ*, the anterior surface of the heart was made up of the right chambers while the left ventricle was barely visible, cases 17, 24, 42, 43 and 62 are examples The apex of the heart was often formed by the right ventricle (cases 33, 42, 49, 54, 57, 58, 60 and 61 are examples) It was due to the enormous size of the right atrium that the anterior atrioventricular sulcus was found to correspond approximately to the median line, it might even lie to the left of it The conus arteriosus of the right ventricle bulged forward, to the left and upward, often reaching the second intercostal space

The weight of the heart, when stated, was practically always increased In proportion to the enormous size of almost all of these hearts, this increase must be considered as moderate only The average weight of the heart in nineteen patients above the age of 14 years (cases 3, 7, 9, 11, 15, 16, 17, 18, 20, 23, 26, 44, 47, 48, 51, 53, 56, 61 and 62) is 574 Gm, the maximum weight being 1,035 Gm (case 16) and the minimum being 250 Gm (case 11) The last-mentioned case was the only one in this series with a normal value In considering only those cases in which either no valvular disease (cases 9, 20 and 44) or one of only slight degree (cases 3, 11, 26 and 53) was found, or in which there was only a question of a valvular deformity (cases 23 and 47), the average weight was somewhat lower (469 Gm) There was evidence that in this group of sixty-two cases, hearts with a relatively small defect showed less enlargement than hearts with a very large defect It was necessary to give due consideration to the degree and number of pathologic conditions of the valves, which were commonly present Seven cases with a defect of 1.5 cm or less in diameter, against five cases with a defect of 4 cm or more in diameter, have been tabulated

The size of the pulmonary artery (the trunk and the orifice) and the aorta (the ascending aorta and the orifice), as well as their ratio, was studied The final figures are given in table 4 Besides the cases in which actual measurements were given, statements of a descriptive character were made in a number of other cases In no case was the pulmonary artery or its orifice described as small In five cases the pulmonary artery was described as "normal" or "normal in size" (cases 9, 22, 29, 36 and 60), but it was also stated in every case that the pulmonary artery was larger than the aorta The pulmonary artery was described as large and the ascending aorta as small, or the pulmonary artery was said to be definitely larger than the aorta in twelve cases (cases 2, 8, 17, 24, 26, 27, 37, 38, 42, 50, 54 and 55) In no case was the ascending aorta or its orifice found to be larger than the pulmonary artery or its orifice The ascending aorta was described as larger than normal in two instances (cases 16 and 20), but it was smaller than the pulmonary artery One of the patients (case 16) showed coarctation of the aorta In six

instances the aortic orifice or the ascending aorta was described as normal in size (cases 18, 37, 40, 41, 49 and 57), but it was always smaller than the pulmonary artery. In conclusion one may state that the pulmonary artery was always larger than the aorta, the average ratio being 3/2. The absolute figures for the pul-

TABLE 3—*The Size of Defect and Kind of Lesion Compared with the Size and Weight of the Heart*

Case	Size of Defect	Valvular Lesion	Size (Weight) of Heart
11	1 cm	None	250 Gm
12	1 by 1.5 cm	Double mitral and aortic lesion	Enormous
17	1 by 0.8 cm	Mitral stenosis and slight aortic regurgitation	480 Gm, marked enlargement of the right side of the heart
22	1.5 cm	Mitral stenosis and regurgitation	Size of a man's fist
33	Size of thumb	None	Moderately enlarged
39	0.9 cm	None	Height, 10.5 cm, width, 13.5 cm
59	1 by 1.5 cm	Endocarditis of the mitral valves	Height, 8.5 cm, width, 11.5 cm, thickness, 7.5 cm
18	3.7 by 5.3 cm	Mitral stenosis, tricuspid regurgitation	385 Gm, length, 15 cm, width, 13 cm, auricles, large
21	5 by 3 cm	Mitral regurgitation, tricuspid regurgitation	Circumference of the heart, 47 cm
34	5 by 5 cm	Pulmonary regurgitation	Enormous enlargement, especially of the atria, length, 16 cm, width, 12.5 cm, depth, 10.5 cm
41	5.5 by 4 cm	Thickening of one pulmonary valve, thickening of edge of mitral valve	Enormous enlargement of the right cardiac chambers, length, 12 cm, width, 12.5 cm, depth, 10.5 cm
53	4 cm	Slight lesion of the mitral and tricuspid valves	545 Gm, marked dilatation and hypertrophy of the right side of the heart

TABLE 4—*The Size and Ratio of the Pulmonary Artery and the Aorta*

	Average for Ten Cases	Maximum	Minimum
Pulmonary orifice	8.2 cm {cases 1, 16, 22, 23, 26, 36, 48,	10.6 cm (case 16)	6.0 cm (case 36)
Aortic orifice	5.4 cm {56, 59 and 61}	7.0 cm (case 61)	4.0 cm (case 56)
Ratio of the pulmonary orifice and the aortic orifice	1.5/1	2/1 (case 48)	1/1 (case 61)
Average for Nineteen Cases			
Pulmonary artery	9.2 cm {cases 6, 7, 10, 13, 15, 18, 20, 21, 33, 34, 40, 41, 43,	15.7 cm (case 40)	5.0 cm (case 60)
Ascending aorta	6.0 cm {49, 56, 58, 59, 60, and 62}	8.0 cm (case 58)	4.4 cm (case 6)
Ratio of the pulmonary artery and the ascending aorta	1.5/1	2.7/1 (case 33)	1.1/1 (case 60)

monary artery were usually far above the average normal figures, a normal size was rarely encountered. The absolute figures for the aorta were usually below the average normal figures but occasionally reached them, i. e., the pulmonary artery was usually large or very large, the aorta was more often small but occasionally normal in size.

The dilatation of the pulmonary artery and of its branches may reach enormous degrees. The trunk was described as aneurysmal (cases 8 and 61), it had a circumference of more than 15 cm in three cases (7, 16 and 40). The branches of the pulmonary artery, if mentioned in the description, appeared widened also, partly into the periphery itself (cases 1, 5, 7, 10, 20, 23, 33, 38, 40, 41, 54, 56, 59 and 62). The following figures may serve as an example. Left branch 3 cm in diameter and two right branches of 2 and 2.5 cm, respectively (case 40), a left branch of 1.8 cm, and a right branch of 1.7 cm (case 62). An example of aneurysmal dilatation of the branches may be cited (case 56), the left branch being 7 cm and the right branch 4 cm in diameter. Enlargement of the pulmonary veins was also reported (cases 8, 38, 40 and 57). In addition to the findings of dilatation, changes in the wall of the pulmonary artery and its branches were not uncommon. Thickness of the wall was found (cases 3, 17, 24 and 34), the wall was abnormally thin, in parts or in toto (cases 7 and 36). Atheromatous changes were noted (cases 7, 24, 26, 38, 49, 51, 54, 55 and 62), with chronic thrombosis (cases 56 and 57) and with chronic thrombosis and endarteritis (cases 14 and 61). The wall of the aorta was described as being unusually thin and flexible in six cases (18, 24, 29, 34, 56 and 60).

As seen in situ, the aorta appeared as a rather small vessel between the superior vena cava at the right and the pulmonary artery at the left. The pulmonary artery, as a rule, took a more horizontal course from the front to the back, being displaced upward by the enormous conus arteriosus.

A typical description of subacute bacterial endocarditis was not found. Ulcerous endocarditis with septicemia was found once (case 22) and milder forms of acute endocarditis five times (cases 7, 15, 18, 52 and 61). The margins of the interatrial defects remained free from these processes.

Chronic pericardial disease was found in only one instance (case 29), and here it was combined with an extensive tuberculosis of the lungs.

Crossed embolism was described only once (case 24).

Active tuberculosis of the lungs was reported in two cases (cases 11 and 29).

Malformations besides those in the cardiovascular system were mentioned in six cases. They consisted of accessory spleens, absence of one ovary, malformed kidney, smallness of one lung, a left lung consisting of three lobes, abnormal shortness of the small and large intestine and bony anomalies of the ribs, sternum and finger.

Roentgenologic Findings—Fifteen patients were submitted to a roentgen examination (cases 33, 35, 42, 43, 45, 46, 49, 50, 51, 55, 56, 57, 60, 61 and 62). The following results were obtained from studying the illustrations or the descriptions, some of the latter being extremely incomplete. The cardiac shadow always appeared enlarged, sometimes to enormous degrees. This enlargement extended to either side but was predominantly to the left, so that the left lower contour sometimes reached the cage of the left inner thoracic rib. The general configuration was globular with a more or less marked prominence in the region of the conus pulmonalis and the pulmonary artery (cases 33, 42, 43, 49, 50, 51, 55, 56, 61 and 62). Absence of enlargement was noted in two cases, in one case (case 45) neither an illustration nor postmortem measurements were given, and in the second case the pulmonary artery was actually found in postmortem examination not to be enlarged (case 60), the aorta was smaller than the pulmonary artery. The main branches of the pulmonary artery form the "hili" in the roentgenogram. They were noted to be enlarged or much enlarged in eight cases (33, 42, 49, 51, 55, 56, 57 and 62). In two cases marked pulsations of the pulmonary artery were observed, but neither organic nor relative regurgitation of the pulmonary valves was men-

tioned in the postmortem report (cases 33 and 43, and Assmann's case 2) The hilar vessels were described as not enlarged in the roentgenogram in one case (case 43), but no actual postmortem measurements were given These hilar vessels, mainly corresponding to the branches of the pulmonary artery, appeared rather sharply defined A low position of the diaphragm was noted in several of the illustrations and was definitely seen in my case

Electrocardiographic Findings—These were available in seven cases (cases 35, 46, 50, 51, 55, 56 and 62) One could expect an axis deviation to the right In five cases readings were made or were possible, and the deviation was present in cases 35, 46, 55, 56 and 62 But only in one case was it as marked (case 56) as, for instance, in pulmonary stenosis In the other four cases it was present only in moderate degree

Clinical Findings—A definite history of rheumatic disease was found in eight cases (5, 14, 31, 33, 37, 50, 52 and 62), a small number as compared with the high figure for chronic valvular lesions met with in cases of interatrial septal defect

No uniformity existed in the duration of symptoms of disturbed circulatory function In twenty of the sixty-two cases, no description was given In seventeen cases, the duration was less than one year, usually it lasted a few months In twenty-five cases a year or more elapsed between the appearance of symptoms and death As to the cause of the onset of lethal cardiac failure, influenza seemed to play a definite rôle in five cases (cases 31, 41, 44, 50 and 55)

It has already been shown that in a number of cases higher age groups were reached The patients withstood well surgical procedures as well as pregnancies Anesthesia to operate on cancer of the penis (case 13) and amputation of the cervix uteri (case 20) were well supported Nine patients bore one child or more (cases 12, 28, 29, 30, 36, 38, 50, 51 and 54) At the time of death, the youngest patient was 32 years old and the oldest 74, the average age was 52.3 years The average number of childbirths was 4.7 One patient (case 12) had eleven children, one (case 54), ten, one (case 38), seven, and one (case 50), six The patient in case 50 became worse during a seventh pregnancy and died during it

Hemoptysis and hoarseness were occasionally observed Hemoptysis (cases 42, 56 and 57) was not necessarily connected with the presence of mitral stenosis (case 57) or cyanosis (case 42) Hoarseness (case 56) was probably well explained by aneurysms of the pulmonary artery (recurrent paralysis of the laryngeal nerve), but it was also present when there were only a moderate dilatation of the pulmonary artery and absence of disease of the mitral valve (case 43)

As to the presence of cyanosis, the common occurrence of lesions of the mitral and tricuspid valves as an influencing factor must be remembered No statement as to cyanosis was made in nine cases In thirteen cases cyanosis was not present (cases 12, 20, 21, 22, 25, 27, 29, 30, 31, 34, 37, 42 and 59) In the other forty cases it was present at least at some time during life The duration of the cyanosis was mentioned in twenty-five of the forty cases In about half of them the cyanosis was of long standing and in the other half of short duration, sometimes only of terminal character The intensity of the cyanosis was mentioned in twenty-six of the forty cases In about half of them the cyanosis was mild, and in the other half intensive, occurring occasionally as a terminal symptom In the group in which absence of valvular lesions was definitely stated (cases 9, 20, 36, 39 and 46) there were two instances of absence of cyanosis (cases 20 and 36), two instances of cyanosis of long duration (cases 9 and 46) and one instance of terminal cyanosis of short duration (case 39) Pallor was mentioned fourteen times (cases 1, 11, 12, 21, 24, 25, 26, 28, 33, 37, 40, 55, 58 and 62), in seven of which

cyanosis was also present. Between the pallor and the size of the aorta there was no close relationship, the size of the aorta was normal in some instances (cases 1, 37, 40 and 58) and small in others (cases 21, 25, 26, 33, 55 and 62). Physical underdevelopment, however, was closely associated with pallor (cases 1, 24, 25, 33, 40, 55 and 62). Numerical blood counts and/or hemoglobin determinations were recorded in nine cases. The figures were above the normal standards in one case (case 61), in another case they were normal on first examination and later higher (case 56), in three cases anemia was present (cases 25, 36 and 46), the rest of the values are normal (cases 35, 47, 55 and 62). Clubbing was mentioned six times (cases 9, 23, 48, 56, 60 and 61) and was always found to occur with cyanosis. Absence of clubbing was present in five cases.

A definite venous pulse in the veins of the neck and/or of the liver was described in twelve cases (cases 1, 4, 15, 19, 37, 43, 44, 51, 55, 56, 57 and 62), in four of which no organic valvular lesion was mentioned in the postmortem report (cases 1, 43, 44 and 57).

A definite precordial bulge was described twelve times (cases 5, 8, 12, 18, 21, 33, 34, 36, 40, 55, 57 and 62) and stated to be absent once (case 60). Pulsatory lifting of the entire chest or at least of the whole precordium was present eight times (cases 5, 15, 16, 19, 33, 53, 55 and 62). The findings in the apical region were different. The apical beat sometimes appeared to be broadened and not located precisely (cases 10 and 33), once it showed retraction, with normal pericardial conditions at postmortem examination (case 8), and often it appeared well circumscribed and resistant (cases 18, 40, 49, 50, 55 and 62). Marked systolic retractions of a number of intercostal spaces, with normal pericardial conditions at postmortem examination, were observed (case 62).

In eleven cases the radial pulse was described as small or hardly palpable (cases 3, 4, 9, 14, 23, 28, 32, 44, 49, 55 and 62), in about half of the cases mitral stenosis was present (cases 4, 28, 32, 49, 55 and 62). In one case the radial pulse was said to be rather full (case 5), here fenestration and thickening of the aortic valves was also reported. The presence of a small pulse in the periphery was sometimes associated with a small aorta (cases 23, 32, 55 and 62) and sometimes not (cases 44 and 49). Blood pressure readings were reported in twelve cases (cases 36, 42, 45, 46, 48, 49, 50, 53, 55, 56, 61 and 62). In six of these cases the systolic figure was 110 or less, the lowest pressure was 96 systolic and 62 diastolic (case 46). In the two cases with high blood pressure, one patient presented chronic interstitial nephritis and coarctation of the aorta (case 36) and one was in a higher age group (59 years, case 53).

The rhythm of the heart, usually indicated by the pulse, was stated in thirty-seven cases. A regular rhythm was noted nine times (cases 22, 32, 35, 36, 40, 45, 54, 55 and 56), an electrocardiographic record was given in three cases (35, 55 and 56). A definite lesion of the mitral valve was present in four of these cases (22, 32, 55 and 56). An irregular or abnormal rhythm was reported twenty-eight times (cases 1, 2, 4, 5, 8, 12, 15, 16, 17, 19, 24, 27, 28, 31, 37, 38, 39, 41, 42, 44, 46, 48, 49, 50, 51, 53, 57 and 62). In three cases observed over a longer period the rhythm was regular but later became irregular (cases 1, 12 and 62). In twenty-two of the twenty-eight cases (78.6 per cent) a valvular lesion was found at postmortem examination (cases 2, 4, 5, 12, 15, 16, 17, 19, 24, 28, 31, 37, 38, 41, 42, 48, 49, 50, 51, 53, 57 and 62). An electrocardiogram was given in seven cases. It showed regular sinus rhythm three times (cases 35, 55 and 56), premature beats (cases 50 and 51), auricular flutter once (case 46) and auricular fibrillation once (case 62).

Statements as to the character of the pulmonic second sound were missing in a number of cases. In others replacement by a diastolic murmur was reported. An accentuation of the second sound over the pulmonic area was reported thirteen times (cases 4, 8, 16, 18, 22, 33, 42, 43, 49, 55, 56, 61 and 62). Of these cases eleven showed a definite and two a probable lesion of the mitral valve. In two instances (cases 8 and 43) a mitral lesion was absent. The pulmonic second sound was described as weak or absent in three cases (9, 12 and 25). In one of these (case 9) there was no valvular lesion, in an other (case 12) aortic stenosis and regurgitation were found, and in the third (case 25) no statement as to the valves was made.

Murmurs were noted in the great majority of cases. Presence of murmurs was recorded in fifty-two cases and absence in five, no statements were made in four cases, and in one case there was "no definite murmur." In forty-one of the fifty-two cases there were one or several valvular lesions present (cases 4, 5, 7, 11, 12, 13, 15, 16, 17, 18, 19, 21, 22, 24, 26, 27, 28, 30, 31, 32, 33, 35, 37, 38, 40, 41, 42, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61 and 62). Thickening of the pulmonary valves as a single lesion was reported once (case 8). In six more cases a partial or no description of the valves was given (cases 23, 25, 29, 45, 47 and 60). The description of an old case (1 [1826]) was very short. In one case "no definite murmur" was reported, and there was no valvular lesion (case 44). All of the four cases in which there was no statement as to murmurs (case 2, 3, 6 and 34) showed valvular lesions capable of producing murmurs.

Three cases remain (cases 9, 36 and 46) for a more complete discussion, and two cases are added from another group because of the existence of peculiar murmurs (cases 8 and 57).

CASE 9—The patient, aged 27, was examined eight years before death. There was a bellows-like sound over the base, presystolic rather than diastolic, and the second sound was hardly audible. The short postmortem report stated that a valvular lesion was absent, that the pulmonary artery was of normal size, and that the interatrial septal defect was the size of a five shilling piece.

CASE 36—The patient, aged 26, had a systolic thrill at the base, at the left sternal line and down to the fourth left rib. A loud, harsh systolic murmur with its maximum at the third left cartilage was heard over the entire front of the chest and on the left side of the back. There was a suggestion of an apical presystolic murmur. The postmortem reports stated that valvular lesions were absent, the pulmonary artery was almost normal in size and thin-walled, and there was a moderate degree of coarctation of the aorta (3 cm, as compared with 4.5 cm for the aortic orifice and 4 cm for the portion beyond the point of narrowing). The interatrial septal defect was thumb-sized, and there was fenestration in the valvula foraminis ovalis.

CASE 46—The patient, aged 5 years, had a loud blowing murmur over the entire precordium, which was maximum over the third left intercostal space and which seemed to extend into the diastole. Later the murmur was no longer heard. Postmortem examination showed no valvular lesion, but dilatation of the tricuspid orifice and marked dilatation of the pulmonary artery. The interatrial septal defect was 2.5 cm.

CASE 8—The patient, aged 10 years, had a purring tremor over the area of cardiac dulness and later at the base. There was a loud systolic murmur heard at the base of the heart, to the right of the sternum at the level of the junction of its upper and middle thirds, later this murmur had a peculiar flapping character, especially to the left side. The pulmonic second sound was accentuated. At post-

mortem examination there was found a slight thickening of the pulmonary valves with an enormous enlargement of the pulmonary artery, and mitral regurgitation was also probably present. The interatrial septal defect was 8.9 cm in circumference.

CASE 57—The patient, aged 52, had a thrill at the apex, a systolic-diastolic thrill in the second left intercostal space, a systolic and presystolic murmur at the apex, and a systolic and diastolic murmur over the pulmonary area. At post-mortem examination there was thickening of the tricuspid valves, and to a slight degree, of the mitral valves, there was no involvement of the pulmonary valves, the pulmonary artery was dilated, with atheroma and thrombosis of its wall. The size of interatrial septal defect was 4 by 3.5 cm.

Data on the four cases in which absence of murmurs was reported (cases 10, 14, 39 and 43) are given in table 5. As far as any conclusion is permitted from these few cases, it seems that an absence of murmur may occur with defects of different size and in the presence of dilatation of the pulmonary artery.

A clinical diagnosis was attempted in twenty-one cases in which congenital disease of the heart was considered nine times (cases 33, 35, 36, 45, 50, 51, 55, 60 and 62)—four times in combination with lesions of the mitral valve. The diagnosis

TABLE 5—*Data on Cases in Which Absence of Murmurs was Reported*

Case	Age, Yrs	Size of Defect	Pulmonary Artery	Valves
10	2	1.5 cm	7.3 cm	No description
14	44	Index finger	10.0 cm, endarteritis and thrombosis	Mitral valves slightly thickened
39	50	0.9 cm	8.0 cm (orifice)	No description
43	15	3.0 cm	7.0 cm	Functional tricuspid regurgitation

of an interatrial septal defect was correctly made by Abbott (case 36), and considered in a few more cases (cases 35, 55, 60 and 62). A lesion of the mitral valve was diagnosed fourteen times in twenty-one cases, and in thirteen cases post-mortem examination showed the diagnosis to be correct. Atherosclerosis of the pulmonary artery was diagnosed and proved in postmortem examination in one case (55). The presence of a mediastinal tumor was incorrectly assumed in case 56, and the patient submitted to an operation from which she died. This was due for the most part to an erroneous roentgenologic interpretation, aneurysms of the pulmonary artery were considered as tumors. In two more cases incorrect roentgenologic diagnoses were made, as follows: tuberculosis or tumor of the hilus (case 33), extensive mottling extending from the pulmonary roots and a nonpulsating mass to the right of the heart (case 48).

COMMENT

Different explanations of this anatomic type of defect have been offered. Since narrowness of the aorta is a common finding, it was considered to be the primary lesion (von Rokitsansky). It should lead to an increase in pressure in the left side of the heart and thus bring about persistence of the interatrial communication. In consequence of this, enlargement of the right side of the heart and dilatation of the vessels

of the lesser circulation would occur. To this explanation the objection can be raised that congenital aortic atresia and aortic stenosis occur without interatrial septal defect (Berblinger), that actual narrowness of the aorta may not be present, though the aorta is smaller than the pulmonary artery (cases 18, 37, 40, 41, 49 and 57), and that at an early age (in the new-born, according to Seidel, and at 6 months, according to Carpenter) no difference in the size of the pulmonary artery and aorta was noted, a fact which permits the assumption that the characteristic variation in size takes place during postfetal development. Another explanation is that suggested by Lutembacher that the mitral stenosis is of congenital rather than acquired character. This, during fetal life, would provoke a flow in reverse of the physiologic one, namely, from the left to the right atrium and would prevent the closure of the atrial septum, the blood would finally reach the greater circulation through the ductus arteriosus. Several objections can be made to this theory.

- 1 In cases of congenital mitral stenosis or mitral atresia (observed in the new-born or within the first few weeks of life) the foramen ovale has been found to be almost (Kockel) or completely closed (Ludwig, McIntosh).
- 2 A normal mitral ostium (explicitly stated to be so) was found in the presence of an interatrial septal defect (cases 8, 9, 13, 20, 36, 39, 40 and 46).
- 3 The common occurrence of auricular fibrillation, also observed several times to develop from a regular rhythm, favors the conception that an acquired "rheumatic" disease is superimposed on the congenital malformation.

It seems best to assume that the interatrial septal defect is the primary lesion, and that the characteristic findings of the heart and great vessels are secondary resultants. The assumption would be that a shunt from the left to the right atrium takes place, as a result, the right side of the heart and the lesser circulation would handle an increased amount of blood, whereas the left side and consequently the greater circulation would be deprived of an equal amount of blood, and this condition would continue throughout life. There is no direct proof for this theory (Gignoux, Cramer and Frommel, Dressler and Roesler), but sufficient indirect evidence has been given.

- 1 It has been shown in experiments on animals that the pressure in the left atrium is higher than that in the right (Straub), which would cause a shunt from left to right.
- 2 The size of the right cardiac chambers and the pulmonary artery as a rule exceed by far the size of the left cardiac chambers and the aorta, respectively. This is also found to be the case in the absence of valvular lesions and in the absence of an obstacle in the lesser circulation, which shows that blood in more than the normal amount is flowing through the right side of the heart and through the lesser circulation. It is known that an increased flow per unit of time

is the most effective stimulus to which the heart will respond by hypertrophy and particularly by dilatation (in 1839 Ecker said "The influx of arterial blood into the cavities of the right side of the heart causes an increased function") If the blood shortcircuits, dilatation of the heart and hypertrophy result In the case of a peripheral fistula, the blood passes through both sides, in the case of a central fistula, only a part of the heart is propelling the stream of blood deflected (Holman) and will thus participate predominantly in dilatation and hypertrophy (The fact that the degree of dilatation by far exceeds the degree of hypertrophy was mentioned by Peacock in 1878) 3 A further proof of the increased functional demands in the lesser circulation are dilatation and arteriosclerotic changes of the branches of the pulmonary artery and dilatation of the pulmonary veins Likewise the disproportionately small size of the left ventricle and of the aorta, which is either relatively or absolutely small, is proof of the decreased amount of blood which is available at the left side and which causes a decrease in the functional stimulus for growth (in 1839 Ecker stated, "Such a communication may be the reason that the physiological dilatation of the aorta does not take place, since a noticeable amount of blood flows off to the right side of the heart, the dilatation of the aorta becomes, so to speak, superfluous"), furthermore, the venous fulness as compared with the relative arterial emptiness speaks in favor of the existence of a current from the left to the right atrium (Johnson, 1878) 4 The enormous degree of right-sided dilatation and hypertrophy occurs without an accompanying lesion, quite commonly, however, a lesion of the mitral valve is present, but in that case the degree of the right-sided dilatation is also out of proportion to the mechanical effects of the lesion (Lutembacher) 5 There is sufficient evidence to assume that hearts with a relatively small defect show less enlargement as compared with hearts with a large defect, this also holds true if a valvular lesion is present, provided the degree and number of the lesions are considered 6 The extreme rarity of crossed embolism speaks against the common occurrence of a shunt from the right to the left, likewise it can be said that the complete absence of cyanosis throughout the entire life in a number of cases proves that at least for these cases an extensive shunt from the right to the left does not exist

One may thus characterize the interatrial septal defect as consisting of two elements (1) a congenital arrest of development and (2) an acquired and progressive hydraulic disturbance (Costa)

It is easy to conceive that the addition of a lesion of the mitral valve simply increases the characteristic features of this malformation, in the first place by increasing the pressure in the left atrium In the presence of a button-hole type of mitral stenosis, the tendency of the left ventricle

and of the aorta toward narrowness will be increased. In the presence of a predominant mitral regurgitation, a venous pulse is likely to occur. The size of the left atrium, which is occasionally already enlarged without an accompanying lesion of the mitral valve, will increase. The right ventricle will also add to its already established dilatation and hypertrophy. The influence of pulmonary disease and disease of the tricuspid valve can easily be understood, disease of the aortic valve is not common and occurs only in combination with lesions of other valves.

The prognosis is not bad, when one considers that the average age is 36 years or higher, if the patients who died from causes other than cardiac failure are excluded. For comparison, Abbott's figures for some other types of congenital cardiovascular malformation are: coarctation of the aorta (average age, 36, number of cases, seventy), interventricular septal defect (average age, 42, number of cases, seven), patency of the ductus arteriosus (average age, 29, number of cases, ninety-two), pulmonary stenosis with closed septums (average age, $10\frac{1}{2}$ years, number of cases, nine), pulmonary stenosis with defect of the interventricular septum (average age, $12\frac{1}{4}$ years, number of cases, eighty-three). A certain amount of activity, repeated pregnancies, a higher age incidence and occasionally even hard work for many years (case 16) are possible for some patients, others are incapacitated for shorter or longer periods. It is difficult to prognosticate the interatrial septal defect per se because of the fact that in three fourths of all of the cases, chronic valvular lesions of some degree are found which should aggravate the prognosis. However, in the twelve cases in which the description mentioned absence of valvular lesions (cases 9, 23 and 46) or in which the lack of a positive statement permitted one to assume that at least no marked valvular lesion was present (cases 1, 10, 20, 25, 36, 39, 44, 46 and 47) the average age was 25 years, which is definitely less than the total average of 36. If one leaves out three patients with diseases other than chronic primary cardiac disease, chronic renal disease (cases 36 and 39) and coronary thrombosis (case 47), one obtains an age of only $21\frac{1}{2}$ years as compared with the figure of $32\frac{1}{2}$ years for the corresponding average age of fifty patients, and if one leaves out the two small children (cases 10 and 25) aged 1 and 2 years, respectively, one still has an average of only 27 years. Thus it seems that the combination of the interatrial septal defect with a chronic valvular lesion does not differ in prognosis materially from the uncomplicated interatrial septal defect itself.

The curious relationship of sex in certain congenital cardiovascular defects has been pointed out by White, who used Abbott's material. For certain types, there is no prevalence of one sex over the other, in other types, one sex is predominant. The average ratio in Abbott's

series between male and female was 58.4 per cent 41.6 per cent (859 cases). If one takes Abbott's figures in general and my figures for the interatrial septal defect, one obtains the ratios given in table 6.

Medvei and Roesler pointed out that the pathologic changes in cardiac development may show a hereditary tendency and may be genotypically conditioned. One would have to speculate that certain genes governing cardiovascular development are sex-linked.

One might think that in cases of physical underdevelopment the aorta ought to be small, and that in cases in which the development is normal the aorta ought to be of normal size, granting thereby the range of variation in the size of the aorta. Of the twenty-one cases in which there was physical underdevelopment, measurements of the aorta were given in thirteen cases. In eight of them the aorta was too small (cases 6, 33, 42, 48, 55, 59, 61 and 62), in five of them the figures were within the normal range (cases 10, 23, 40, 41 and 49). Of

TABLE 6—*Sex Incidence of Congenital Cardiovascular Defects*

Type of Lesion	Number of Cases	Per Cent Male	Per Cent Female	Comment
Patent ductus arteriosus	84	34.5	65.5	} Female sex predominant
Interatrial septal defect	62	38.3	61.7	
Coarctation of the aorta	68	78.0	22.0	} Male sex predominant
Anomalies of semilunar cusps	39	87.2	12.8	
Pulmonary stenosis	105	55.2	44.8	} No or negligible predominance
Defects of interventricular septum	58	50.0	50.0	

the seven cases in which there was a normal physical development, measurements were given in three cases. In each of them the figures were within the normal range (cases 18, 22 and 60).

There were only a few cases which did not seem to fit into the classic picture. In one case the size (case 22) was described as that of a man's fist, however, the description mentioned right ventricular dilatation and hypertrophy and it was stated that the heart was kept in alcohol for a long time before the measurement was taken. In another case (case 11) the heart weighed 250 Gm., but the volume of the right side of the heart was said to equal that of the left. And in a third case the right ventricle was described as the only chamber of the heart which remained unaltered in size (case 36). One may assume that in this case the rather small defect, which was only the size of a thumb, permitted only a small amount of shunting, the pulmonary artery was of normal size also (6 cm.), though the aorta was smaller, as one might expect.

It has been mentioned that atherosclerotic changes in the pulmonary artery and its branches are not uncommonly found in this type of congenital cardiac malformation. There are two cases in the literature

of sclerosis of the pulmonary artery in early childhood in which the authors did not realize the causal etiology of the interatrial septal defect. In one case of Linden's, a girl, aged 11 months, had slight cyanosis, first with pure cardiac sounds, and later with a systolic apical murmur, there was accentuation of the pulmonic second sound, and postmortem examination showed the characteristic picture of a large right atrium and ventricle, a very small left atrium and ventricle and a pulmonary artery 40 mm and an aorta 29 mm, in circumference. The foramen ovale was wide open and the ductus arteriosus patent for a probe. The branches of the pulmonary artery were widened, macroscopically and microscopically, and showed cushions in the intima with lipoid deposits. Linden developed the conception that an abnormal narrowness of the pulmonary veins had caused this pathologic condition. In the other case, that of Watjen, a girl, aged 6 months, had a large heart as revealed by roentgenograms and a cough followed by attacks of cyanosis. Post-mortem examination showed an interatrial septal defect, 8 by 11 mm in size, and an interventricular septal defect, 10 by 4 mm, the great vessels were transposed. The right ventricle was small and gave off the aorta, which measured 24 mm, the left ventricle was twice as large as the right and gave off the pulmonary artery, which measured 40 mm. All of the branches of the pulmonary artery were widened, the arterioles showed microscopically an obliterative intimal proliferation with lipoid deposits. Watjen's idea as to how the shunt worked is objectionable, but he stated correctly that the functional mechanical overburdening in the lesser circulation caused the proliferation of the intima.

There are several facts concerning the occurrence of valvular lesions which are of interest, but a well founded explanation cannot be offered. First of all, the frequency of their occurrence is striking (three fourths of the cases studied here showed valvular lesions of varying degrees). This number exceeded by far what has been observed in other types of congenital cardiovascular malformations. The actual number of lesions was undoubtedly even greater, since many of the descriptions were not detailed enough and since in a few of the cases no statements as to the valves were made. Second, there was absence of subacute bacterial endocarditis, although this condition is not at all rare in other types of congenital cardiovascular malformations (Abbott). In this series, about 10 per cent of the patients had acute endocarditis and less than 2 per cent (1 patient) died of it. In her recent series of one thousand cases, Abbott found that of fifty patients with an uncomplicated defect at the base of the interventricular septum twenty-one had acute endocarditis, thirteen of whom died of the bacterial infective process. The corresponding figures for ninety-two patients with patency of the ductus arteriosus were twenty-one and twenty-one. Acute endocarditis occurred in nine of twenty-five cases of pulmonary stenosis with a

closed ventricular septal defect. If one assumes that a "rheumatic" etiology was the underlying cause of the valvular diseases, one wonders why chronic pericardial disease was practically absent. It was found in only one case in which there was also chronic extensive tuberculosis of the lungs. On the other hand, complete irregularity of the heart was frequently noted and in most cases probably meant auricular fibrillation. It is easy to imagine that a constant overburdening leads to fibrotic endocardial changes, this hypothesis would be more easily applicable to changes in the tricuspid and pulmonary valves. It is rather difficult to explain changes in the mitral valve on this basis, especially if a buttonhole mitral stenosis is found. No mechanical explanation of this sort would hold true for lesions of the aortic valve.

Though it seems probable that the size of the defect may influence the size of the heart in general, it is difficult to prove it. One would have to show that in the presence of small openings, which are actually open, i. e., have no valvelike character, the hearts keep to a normal or almost normal size. Four cases can be cited which showed no defects or lesions other than the opening. Markham told of a child, aged 4 years, in whom the foramen ovale permitted the point of a finger to pass but was partly narrowed by a membranous valve, the heart was normal in every aspect. Foster reported the case of a child, aged 2 years, in whom the aperture was the size of a goose quill, the heart and the great vessels were normal except for a slight degree of hypertrophy of the right atrium. Moul's reported the case of a child, aged 3 months, in whom the aperture would receive a pencil, the ventricle and the large vessels were normal. Ohm had a patient, aged 16 years, in whom the foramen ovale was open far enough to receive a thick probe, the heart was twice as large as the fist, and all of the cardiac chambers were dilated. Thus Ohm's case does not fit into the aforementioned theory. If the interatrial septal defect becomes large, one is finally faced with the *cor triloculare biventriculosum*, here, however, one can no longer speak strictly of a defect, and the mechanics are most probably also different.

There is no unusual tendency noted for the development of tuberculosis of the lungs, the rich supply of blood to the lungs resulting from the mechanics of this condition (in contrast, for instance, to pulmonary stenosis) as well as the frequent occurrence of lesions of the mitral valves can be accounted for.

Assmann described the important roentgen findings, they consist of an unusually small aortic knob, a prominent pulmonary arch, wide hilar vessels and an enlarged, globular heart. The enormous enlargement of the hilar vessels has been misinterpreted roentgenologically, tuberculosis and tumor being the two main erroneous diagnoses. In

one case (Wahl and Gard, case 56) the report of the roentgen examination seemed to support the final diagnosis of mediastinal tumor, since the observed masses were sharply defined and did not pulsate. The patient bled to death when the mediastinal mass was incised. Postmortem examination showed that the branches were of spheroid shape and were filled with thrombotic masses. Each of the roentgenologic characteristics taken per se may be found in other pathologic conditions also. The absence of the aortic knob (at the left side) is seen in enormous enlargement of the pulmonary artery due to any etiology, in marked mitral stenosis, in coarctation of the aorta and in cases in which the aortic arch crosses the right bronchus (right-sided aortic arch). Enlargement of the pulmonary artery and of its branches occurs occasionally in the presence of certain other congenital anomalies, such as patency of the ductus arteriosus and interventricular septal defect, or it is due to primary degenerative processes (atherosclerosis and arteriosclerosis) or to syphilitic or mycotic disease. Increased pulsations of a moderate degree need not be an expression of valvular regurgitation, though it is difficult to exclude functional incompetency. An increased pulse pressure in the lesser circulation and/or pathologic changes of the wall seem to be able to produce this roentgenologic symptom also. Lutembacher stated that the wooden shoe-like shape (*cœur en sabot*) was an important point in the roentgenologic part of the diagnosis, and Cramer and Frommel, as well as Muller, accepted his conception. Lutembacher's belief was merely theoretical, because in his case no roentgenologic study was made. Actually, neither the published pictures nor my case showed evidence of the *cœur en sabot*. This shape is due to a break in the contour of the left side of the heart because it is formed by both ventricles, the right ventricle below and the left ventricle above (Raab, Roesler), it is also best seen in cases in which the right ventricular hypertrophy predominates over the dilatation, as in pulmonary stenosis. In the interatrial septal defect the silhouette of the heart varies in shape from oval to globular, and the contour of the left side of the heart is almost entirely formed by the right ventricle, the right ventricle remaining above and the left ventricle below (and mainly posteriorly). The fact that even enormous degrees of right ventricular enlargement may express themselves as a predominant enlargement of the cardiac shadow to the left is not fully appreciated in the roentgenologic literature, but a study of the postmortem situs will often show that the enlargement of the right ventricle is predominantly or entirely to the left of the median line. Scarcely any studies have been made in the oblique positions to determine the size of the left atrium, but, as my case shows, definite enlargement has been demonstrated and must be expected quite often, though this diagnostic feature does not help in the diagnosis of the interatrial septal defect.

proper The low position of the diaphragm may be understood in a twofold way First, a large, heavy heart depresses the diaphragm by its weight, it may be recalled that the postmortem weight of all of these hearts was definitely less than the actual weight during life because of the large volume of blood in them If the pressure lasts predominantly in the central portions as one sees it in the presence of a large right ventricle (and also in the presence of an aneurysmal dilatation of the left atrium), the depression affects the entire diaphragm equally, whereas in predominating enlargement of the left ventricle only the left leaf is markedly depressed Second, this low position is an expression of physiologic adaptation, the space available for the lungs is actually so narrowed down by these tremendous hearts that the mechanism of lowering the diaphragm seems to be the only way to guarantee a certain expansion for them

In all of the five cases in which the electrocardiographic study permitted the degree of axis determination, a marked anatomic predominance of the right side existed, expressed by the size of the hearts themselves as well as by their weights, and it is known that in all of the hearts of this type a counterclockwise rotation of the entire mass of the heart takes place Since in four cases the degree of axis deviation to the right was only moderately marked, it seems permissible to assume that some proof is given hereby that the actual increase in the thickness of the wall plays even a greater rôle in the production of axis deviation than an enormous dilatation with the additional counterclockwise rotation

It is the ordinary picture of cardiac failure which governs the last months or years of the life of the patients, provided death is not caused by an intercurrent disease Peripheral edemas are often but not always reached In the morbus caeruleus type, for instance, in cases of pulmonary stenosis, death may occur rather suddenly It is known, on the other hand, that the course of decompensation in chronic valvular lesions, especially in lesions of the mitral valve, is rather chronic With the interatrial septal defect death is not sudden The course of decompensation may be similar to that of simple chronic valvular lesions or may be of shorter duration, lasting only a few months

Neither analyses of the blood gases nor microscopic studies of the capillaries of the skin are available in any case Therefore any discussion on the cause of the absence, presence and degree of cyanosis (and in partial connection with this problem, any discussion on the absence, presence and amount of intracardiac shunt) is merely speculative If cyanosis, sometimes of an intensive degree, appears only a short time ante mortem, it is spoken of as "cyanose tardive" (Bard and Curtillet, Wallmann, 1852), the assumption being that a raised pressure in the right atrium brings about a shunt from right to left

If this mechanism is to take place, one would have to postulate that the balance between the right and left sides of the heart becomes disturbed (left-sided failure), or that the resistance in the lesser circulation suddenly increases. It is important to realize that the appearance and persistence of cyanosis and its degree will be influenced by concomitant valvular lesions and by arteriosclerotic changes in the pulmonary arterial system. If in a given case cyanosis was mainly brought about by the shunt, one would know that at least one third of the blood was shunted across (Lundsgaard and van Slyke).

The interatrial septal defect shows right-sided dilatation (and hypertrophy) as a leading feature. The pulsatory phenomena of veins and liver as well as of the wall of the chest will therefore commonly demonstrate characteristic though manifold signs of this anatomophysiological fact (Dressler).

The insufficient description and the lack of graphic registration (case 55 is an exception) of the venous and liver pulse make it impossible to state whether a simple systolic pulse or a double-waved, auricular pulse was present. The depression of the pulse wave in the veins and liver corresponds in time to the systolic emptying of the heart and is caused by the diastolic-presystolic emptying of the atria and the ventricular contraction (downward movement of the atrio-ventricular septum and diminution of the volume of the ventricular chambers). Failure of the right ventricle with overfilling of the right atrium, especially in the presence of auricular fibrillation, counteracts this depression in the pulse wave. In cardiac failure the venous blood empties into the right atrium, not, as normally, predominantly during systole but almost entirely during diastole; in congestive heart failure, the venous blood empties only during the beginning of diastole. The result is a systolic pulse, consisting of systolic plateau and a slope in the beginning of diastole. If, however, a regular sinus rhythm persists and the hypertrophied right atrium thus has not lost its action, the presystolic atrial contraction, which finds resistance in the remainder of the blood filling in the ventricle, throws blood back into the large veins, then, in addition to the systolic elevation (which is an expression of congestion) there is added a wave of presystolic regurgitation, and a double-waved pulse results. This type of pulse has been formerly considered as characteristic of tricuspid stenosis (Mackenzie), but it is found in the presence of other conditions also in the combination of mitral stenosis with an open foramen ovale or interatrial septal defect (Jagic, Dressler and Roesler [case 55]), or in concretio cordis (Volhard, Wenckebach), or whenever venous congestion in the greater circulation, right atrial hypertrophy and sinus rhythm are acting together. Mitral regurgitation with an interatrial communication does cause a systolic venous pulse (Reineboth), as is easily understood

from the mechanics in this condition. A systolic or presystolic venous pulse may therefore be found in the presence of the interatrial septal defect with or without an accompanying lesion of the mitral valve. Other conditions, however, give rise to these pulsatory phenomena just as well and may be well combined with the primary congenital malformation, especially congestive failure of the greater circulation and lesions of the tricuspid valve. The marked hypertrophy and dilatation of the right side of the heart, especially of the right atrium, are conditions favorable for the appearance of an abnormal venous pulse.

Systolic propulsions and depressions of the thoracic wall are considered here mainly as being caused by the right side of the heart. The normal apical thrust is caused by the left ventricle and is due to several factors during systole. These are lever-like upward and forward movements of the apical portion, clockwise rotation of the left ventricle, an increase in consistency and, at least in animals, formation of a hump above the apical portion of the left ventricle. Over the precordium, corresponding to the right ventricle, there is often seen slight systolic depression. While enlargement of the right ventricle (hypertrophy and dilatation) commonly will produce a systolic precordial propulsion, pure dilatation as a rule does not, and pure hypertrophy scarcely ever does (Dressler). In enlargement of the right ventricle of considerable degree but without hypertrophy, pulsatory heaving of the lower sternum, however, occurs, as was shown in Hoefler's case, in which there was an interatrial septal defect (case 33) and in which the wall of the enormous right ventricle had a general thickness of only 4 mm. and a thickness of only 6 mm. in the conus area. The systolic propulsion of the lower central portion of the thoracic wall is due partly to change in the shape of the cardiac mass (mainly during the presphygmic period) from a transverse ellipse in cross-section to a cone, and partly to recoil. The latter factor is increased by high pressure in the pulmonary artery and by increased filling of the right ventricle (Lang). As long as the left ventricle is not completely displaced, a normal circumscribed apical thrust may persist. In the presence of considerable enlargement of the right ventricle the front wall of the heart is mainly formed by it (and by the right atrium) and so is the apical thrust, the left ventricle having been pushed away from the wall of the chest. This apical thrust as a rule is not well circumscribed, and a centripetal movement may or may not prevail, depending apparently on how quickly the border of the left lung can fill the available free space. In rare instances however, (in interatrial septal defect, according to Dressler and Roesler), a well circumscribed resistant apical forward thrust can be found, exactly like that in hypertrophy and dilatation of the left ventricle. The explanation for these cases is that the enormous right atrium displaces the large right ventricle to the left, so that the main mass of the right ventricle

no longer corresponds to the precordium but rather to the axillary position. The displacement to the left is aided by the absolute or relative narrowness of the left ventricle, as in many cases of interatrial septal defect. This finding, a well circumscribed, resistant apical thrust in the apical region in the presence of a predominant and enormous right-sided enlargement, is not known for any other clinicopathologic condition. In high degrees of right ventricular enlargement, the systolic propulsion can extend down to and include the apical region, but it rather fades out toward it, this type also is likely to occur in the presence of a small left ventricle. The propulsion of sternum and precordium is especially favored if the heart has a support against the spine, i. e., if it reaches a considerable size and especially if the left atrium is markedly enlarged also (Dressler).

The heart is pressed against the anterior thoracic wall by the atmospheric pressure in the lungs, at its posterior and lateral circumference.

The lung cannot move away from the chest wall, and neither does the heart, unless another freely movable part takes up immediately the newly formed space.

Since the ribs, as stiff parts of the surroundings cannot follow the movements of the heart, it results necessarily that the parts of the heart adjacent to them remain fixed, just as well as the ribs themselves. In all cases where the heart lies in a larger area close to the chest wall the adjacent displaceable chest organs (especially the lungs) will not be able to fill this space with sufficient speed and to the necessary extent, therefore, the heart will remain fixed to the chest wall during all movements (Kiwisch, 1846).

This statement explains how localized depressions of the thoracic wall may be caused by the action of the heart, especially if it faces to a large extent the anterior thoracic wall. Atelectasis of the pulmonary borders, so commonly seen in the presence of large hearts, adhesions and infiltrations, will inhibit the function of the pulmonary cushion (Weltmann). The propulsion of the sternum and precordium acts like an inspiratory movement. Besides this immediate aspiration another mechanism, a mediate aspiration, has to be considered. In certain cases in which there are valvular defects the intrathoracic pressure drops markedly during systole, namely, when a relatively large amount of blood (pathologic increase in the volume per stroke) suddenly disappears from the thoracic cavity, this takes place in aortic and tricuspid regurgitation (Lang), in the latter this sudden change lasts longer because the venous return into the chest is inhibited during systole. If this difference in pressure is unusually marked, the pulsatory phenomena—depression—will extend far beyond the borders of the heart. In the presence of increased venous pressure the venous inflow, however, will more rapidly compensate for the diminution in the systolic intrathoracic pressure. A third cause for depressions of the thoracic wall of the diffuse type is the action of aspiration as caused by the forward bulge of the middle

portions of the anterior thoracic wall. The chest represents a stiff-elastic system. If a pulsatory force sets up a short lasting deformation in one area, movements, though of less intensity, will take place in the surroundings as well as at some distance from this area (Dressler). A propulsion of the sternal portion brings about traction along the lateral portions of the bony thorax, resulting in a flattening out and inward movements of the ribs, usually more marked at the right than at the left side. A propulsion of the right side of the chest, as for instance, that seen in tricuspid regurgitation when the blood is thrown into the right atrium and into the liver, leads to a marked depression of the left side of the chest.

In the presence of these pulsatory phenomena one should consider chronic pericardial disease last and not first, as is usually done.

The right atrium of normal size is nowhere in contact with the thoracic wall, when enlarged it may reach the left sternal border. It seems that it can produce palpatory thoracic movements only if blood is rushed into it with arterial power, as in tricuspid regurgitation.

A correlation of the various actual instances of apical pulsations and those of the thoracic wall in the interatrial septal defect with the facts of this discussion shows that these phenomena can be explained by the finding of a large right side of the heart, and that they will be increased by smallness of the left ventricle, the presence of lesions of the mitral, tricuspid and pulmonary valves, increased pressure in the lesser circulation and thin, elastic thoracic walls—conditions commonly present in the interatrial septal defect.

The epigastrium frequently shows pulsations, namely, a systolic depression, this is due, first, to the systolic volumetric diminution of the liver and, second, to the systolic upward pull of the left lobe of the liver. A systolic forward bulge is usually due to a ventricular pulse of the liver, on account of congestion or regurgitation. Systolic pulsations of the abdominal aorta occasionally may be seen and felt, and in rare cases the enlargement of the right ventricle may produce a systolic heaving in a small area between the xyphoid process and the left costal arch. Pulsations of the extent observed in my case are unique. In this case the tremendous right ventricle had displaced the diaphragm downward to an enormous degree, as clinical, roentgenologic and anatomic observation showed.

The small volume of the peripheral pulse and the occurrence of a rather low blood pressure may be in connection with a decreased output of blood into the greater circulation and with an underdevelopment of the arterial system.

The number of cases in which a graphic registration would permit the exact recognition of the type of irregular or abnormal rhythm is

small, but it is probable that auricular fibrillation was present in the majority of these cases. The descriptions often mention total irregularity, irregularity over prolonged periods or irregularity occurring in the later stages of the disease, and in more than three fourths of these cases there is a chronic lesion of the mitral valve as a postmortem finding. It is only logical to assume that a causal relationship exists between the "rheumatic" process and the occurrence of auricular fibrillation. The interatrial septal defect thus takes on a unique feature among the congenital cardiovascular malformations. In Roesler and Kiss' electrocardiographic study of one hundred patients with congenital cardiac disease, including all age groups up to the fifth decade, there was no incidence of auricular fibrillation, the same was true for Wedd's twenty-six patients, aged 18 and above, and for Irvine-Jones' one hundred children. The few cases in which auricular fibrillation was present (McCulloch's case 11, Krestin) showed definite evidence of rheumatic disease also.

One probably may expect the pulmonic second sound regularly to be accentuated. This, however, is not always the case. Its common occurrence in the presence of a lesion of the mitral valve deprives it of much of its value as a diagnostic sign.

It can be stated that an interatrial septal defect may exist without giving rise to a murmur (Chiari, Elbogen, Ménétrier and Wolff and Hotz, case 2). The question as to whether the interatrial septal defect produces a murmur is more difficult to answer. After many cases had been excluded by the former analysis there remained a few for discussion. In Peacock's case (8) one wonders how much connection the basal murmur may have had with the thickening of the pulmonary valve and with the enormous dilatation of the pulmonary artery, since it is known that the passage of blood from a vessel of a relatively narrow caliber to one of much greater caliber may cause a murmur, on the other hand, this murmur was best heard to the right of the sternum. In Abbott's case (36) there was coarctation of the aorta, and in this anomaly murmurs are well known to occur, partly in connection with the collateral circulation and in the back, where the murmur was present in this case. Whether murmurs exist or not with this moderate degree of coarctation cannot be stated in general. In Costa's case (57), there arose a question as to whether the thrills and murmurs over the pulmonary area might not simply have been caused by a functional pulmonary regurgitation and by the extensive changes in the walls of the pulmonary artery. Johnson's case (9) and Amberg and Willius' case (46) offer little argument except that there was a short description of postmortem findings in the former, and in the latter the presence in a child of a murmur with its maximum at the left of the base may

not be characteristic. One is indeed reminded of the statements of the two authors, Markham and Potain

In all cases of open foramen ovale hitherto met with in which bruits have been heard during life, there have been found (where examinations have been made after death) in addition to the open foramen ovale, abnormal conditions in other parts of the heart, or of the great vessels, such as of themselves might be considered sufficient to produce the unnatural sound (Markham, 1857)

J'en dirai autant de la communication interauriculaire par persistance du trou de Botal. Elle paraît incapable de déterminer un bruit de souffle quelconque, car, lorsque cette lésion est isolée, elle ne s'accompagne d'aucun bruit normal, et je ne connais pas une seule observation où le souffle qui lui a été attribué ne pût recevoir une interprétation meilleure. Le volume de l'onde, sanguine est sans doute ici trop minime et la force de projection trop petite. (Potain, 1894)

(I shall say as much for the interauricular communication through persistence of Botal's foramen. It seems incapable of producing any murmur because, when this is an isolated lesion, it is not accompanied by any normal bruit, and I know of no observation in which the murmur that was attributed to it could not receive a better interpretation. The volume of blood is undoubtedly too small and the projecting force too weak in this instance.)

One could think that in cases in which the interatrial opening has a smaller caliber than that dealt with in my series there is more likelihood of the appearance of a murmur. And indeed, there are several cases to be cited. Apparently they do not present an interatrial septal defect proper but stages in the closure of the foramen ovale or persistence of an incomplete union of the valvula with the septum (Patten), they are given in table 7. Carpenter's case probably may be discarded, considering the type of murmur present and the age.

It may be stated that there is some evidence, though not final, that a murmur may occur owing to the presence of an interatrial septal defect. It should be best perceived over the sternum, at about the level of the third rib. It is usually systolic, but may start in or extend into the diastole, it should not be transmitted into the vessels of the neck. Almost the same conception was expressed by Gignoux. It seems that there would be no diagnostic significance if it is heard to the left of the sternum, because it could not be differentiated from murmurs caused in the area of the pulmonary orifice or the pulmonary artery. Theoretically it is possible that the murmur could be heard to the left of the median line, since it has been pointed out that the right side of the atrium may extend that far to the left. Lauby and Pezzi pointed out that there would hardly be a possibility of transmission to the thoracic wall because the murmur, naturally of short duration and of little intensity, would take place in the left atrium, which is deeply situated, especially on account of the enormous right-sided enlargement. As one may assume that a murmur is produced at the level of the defect, their argumentation is correct. The distance of the interatrial septal

defect from the anterior thoracic wall is marked. If the conception of the shunt from left to right is correct, the murmur will be transmitted into the right atrium, however, and not into the left atrium. Abbott and Weiss pointed out that this murmur is liable to be manifest at the point of the precordium where the right chambers most closely approximate the thoracic wall.

Of historical interest is the reasoning of some of the authors as to how and during which phase of the cardiac cycle this murmur

TABLE 7—*Cases Representing Stages in the Closure of the Foramen Ovale but Not an Interatrial Defect Proper*

Author	Age, Years	Size of Defect	Size of Heart	Valves	Pulmonary Artery	Murmurs	Comment
Markham	7	Point of finger	Normal	Normal	No statement	Rough, loud systolic bruit at the base and in the left subclavian region, later on over the whole precordium	Death due to miliary tuberculosis
Foster	2	Goose quill	Right atrium slightly hypertrophied and dilated	Normal	Normal	Systolic murmur at third left rib next to the sternum, variable in intensity	Cyanotic since birth
Mouls	$\frac{1}{4}$	Pencil	Normal	Normal	Normal	Presystolic midsternal murmur	Pale, underdeveloped, bronchopneumonia
Ohm	16	Thick probe	Enlarged	Normal	No statement	Systolic and diastolic murmur at apex and base, sometimes also presystolic, changing in intensity and character	Pale, cyanotic and underdeveloped, cerebral embolus
Carpenter	$\frac{1}{2}$	$\frac{1}{4}$ inch	Right atrium hypertrophied and dilated	No statement	Normal	Rough systolic murmur, maximum in second left intercostal space, not transmitted to the back	

should take place. Markham thought that because the murmur in his case was perceived during ventricular systole, it must have been coincident with atrial diastole, during the atrial systole the pressure would be equal in both atria, and therefore no tendency of blood flow from one to the other would exist. During atrial diastole the blood rushes from the vena cavae and pulmonary veins into the relaxed atria and finds its way through the foramen and may under certain conditions conceivably produce vibrations. The murmur in Johnson's case was a presystolic one. He felt that the right atrium would empty itself less completely during atrial systole than the left, in consequence of the

influx of blood from the left side. Then during the succeeding atrial diastole some blood would flow from the partially filled right atrium into the left one. Thus there would be a to and fro tidal flow of blood through the foramen ovale, an active propulsion of arterial blood to the right during the atrial systole and a passive flow of venous blood to the left during atrial diastole. In Ohm's case there was a systolic and diastolic basal (and apical) murmur. The systolic murmur was thought to be caused by the back-flow of blood through an incompetent mitral orifice (the heart was enlarged) which on being pressed through the foramen ovale would cause vibrations, perceived as a systolic murmur, while during ventricular diastole the overfilled left atrium would empty rapidly (more rapidly than the right atrium), suction would draw blood from the right into the left atrium, and the vibrations would cause the diastolic murmur.

That many of the clinical signs and symptoms in the presence of an interatrial septal defect occur in other types of organic cardiac disease was clearly stated by Ecker in 1839.

SUMMARY

A case is reported which illustrates the clinical and anatomic peculiarities of interatrial septal defects. Sixty-two cases have been reviewed, including mine. All of the cases of small defects or complete absence of the interatrial septum and combinations with patency of the ductus arteriosus, pulmonary stenosis, interventricular septal defect and a high grade of coarctation of the aorta have been excluded.

In at least three fourths of all the cases valvular lesions were found which affected predominantly the mitral orifice. Subacute bacterial endocarditis did not occur, chronic pericardial disease, crossed embolism and tuberculosis of the lungs occurred rarely.

Almost all of these hearts were large, they were often of enormous size, even in the absence of a valvular lesion. This was entirely, or almost entirely, due to a right-sided enlargement, dilatation exceeding hypertrophy in a disproportionate degree. The left side underwent relatively little change from narrowness to a moderate increase in size. The average heart weight for nineteen patients above the age of 14 was 574 Gm, and in nine cases of complete or almost complete absence of valvular lesions, 469 Gm. There was some evidence that the size of the heart was influenced by the size of the interatrial defect. The pulmonary artery was always larger than the aorta, the average ratio being 3:2. Expressed in absolute figures, the pulmonary artery was large or very large, but rarely normal in size. The aorta was usually below the normal figures, often being very small and thin-walled. The branches of the pulmonary artery were often dilated, the artery as well as its branches being the seat of atherosclerotic processes. As

seen in situ, the right side of the heart formed the entire front wall, the pulmonary conus extended far to the left and upward, and the aorta was placed between the pulmonary artery and the superior vena cava.

This cardiovascular malformation can be best conceived in its entity by assuming that there was added to the congenital arrest of development an acquired hydraulic disturbance, a shunt from left to right, as a result of which the right side of the heart and the lesser circulation handled an increased, and the left side of the heart and the greater circulation a decreased, amount of blood. The indirect evidences for this theory were given.

The average age was 36 years, the prognosis as to duration of life was about equal with that in coarctation of the aorta, less than that in the interventricular septal defect and better than that in patency of the ductus arteriosus and pulmonary stenosis. Repeated pregnancies, anesthesia and capacity for physical work were well supported in a number of cases, in others, however, chronic invalidism was present. The common combination with chronic valvular lesions did not aggravate the prognosis. There was prevalence of the female over the male sex in the proportion of 3:2, similar to the ratio in patency of the ductus arteriosus.

The clinical course was that of ordinary cardiac failure, lasting for shorter or longer periods, even when all of the cases with valvular complications were omitted. Clubbing was sometimes present. Cyanosis was more often present than not, but the combination with lesions of the mitral and tricuspid valves is to be remembered. Pallor, a small radial pulse and a tendency to a lower blood pressure were rather common. These findings may be understood as an expression of actual arterial underdevelopment and/or a decreased output of blood into the greater circulation. Other clinical findings were an expression of the enormous right-sided enlargement of the heart. These were the precordial bulge, certain features of the apical thrust (circumscribed and resistant, indefinite and systolic retraction), systolic propulsions and depressions of smaller or larger parts of the thoracic wall (important for differential diagnosis from chronic pericardial disease), the occurrence of a systolic or presystolic pulse in the veins and liver, which was influenced by venous fulness, the presence of sinus rhythm or auricular fibrillation, and the occurrence of regurgitation of the tricuspid and mitral valves. Auricular fibrillation was common, in this the interatrial septal defect distinguished itself entirely from all other congenital cardiovascular malformations in which auricular fibrillation was of the greatest rarity. The same cause obviously was responsible for auricular fibrillation and chronic valvular deformity, especially of the mitral orifice. The common occurrence of an accentuation of the pulmonic second sound was mainly an expression of a concomitant lesion of the mitral valve. In the

absence of this lesion accentuation was sometimes present. Murmurs were at times absent. When present, however, they were more commonly due to the combination of valvular lesions. In the absence of lesions, there was still dilatation of the pulmonary artery to be considered with or without changes in the wall and relative insufficiency of the orifice as the cause of murmurs which were probably thought to be characteristic of the defect. If a characteristic murmur of this sort existed, it was midsternal systolic, probably partly diastolic and not accompanied by a thrill.

The roentgenologic findings were those of a large heart varying in shape from oval to globular and extending, as a rule, toward the left. The pulmonary conus and artery projected far to the left, and upward and forward. The branches of the pulmonary artery (the "hili") at times showed increased pulsations and were sharply defined and enlarged. Lack of knowledge of the roentgenologic picture led to the erroneous diagnosis of mediastinal tumor or tuberculosis. The aortic knob was small—at times invisible. Other conditions which caused pulmonary dilatation and narrowness or absence of the aortic knob were given.

The interesting finding from the electrocardiographic study was the presence, as a rule, of only a moderate degree of axis deviation to the right. Enormous dilatation of the right side of the heart with comparatively moderate hypertrophy did not cause a high degree of right axis deviation in the electrocardiogram.

APPENDIX

This is a tabulation of the sixty-two cases arranged consecutively by year.

Case	Year	Author
1	1826	Louis (no. 4)
2	1835	Bouillaud (no. 157)
3	1847	Mayo
4	1862	Petters
5	1864	Huter
6	1875	Rokitansky (no. 7)
7	1875	Coupland
8	1878	Peacock
9	1878	Johnson
10	1880	Chiari
11	1880	Bucquoy
12	1880	Firket
13	1880	Gibier
14	1884	Elbogen
15	1887	Nicolaides
16	1890	Greenfield
17	1893	Butin
18	1894	Jaenike (-Rudolph, 1900)
19	1895	Reineboth

20	1902	Dhotel
21	1904	Seidel (no 2)
22	1904	Soldner
23	1905	Sundberg
24	1907	Ems
25	1909	Popper
26	1909	Sand (no 9)
27	1909	Abbott and Kaufmann (no 2)
28	1910	Lesieur, Froment and Cremieu
29	1910	Gignoux (no 14)
30	1910	Gignoux (no 16)
31	1911	Dufour and Hubert
32	1911	Moureyre
33	1912	Hoeffer
34	1913	Sternberg
35	1915	McCulloch (no 1)
36	1915	Abbott (no 1)
37	1915	Abbott (no 2)
38	1916	Lutembacher
39	1917	Ménétrier and Wolff
40	1920	Zeidler (no 1)
41	1920	Zeidler (no 2)
42	1923	Cramer and Frommel
43	1923	Hotz (no 2)
44	1925	Beattie
45	1926	Villaret, Chaveau and Bariéty
46	1926	Amberg and Willius
47	1926	Mouktar and Sédad
48	1926	Cabot
49	1927	Muller
50	1928	Jonen
51	1928	Langeron and Lohéac
52	1929	Halipré
53	1929	Hammer and Bok
54	1929	Pellicelli
55	1930	Dressler and Roesler
56	1931	Wahl and Gard
57	1931	Costa (no 1)
58	1931	Costa (no 3)
59	1931	Costa (no 4)
60	1931	Costa (no 5)
61	1932	Okkels and Therkelsen
62	1933	Roesler

This is the eleventh article of a series of studies of congenital cardiovascular malformations. The preceding ones, published in German, were

- 1 Roentgen Ray Findings, *Wiener Arch f inn Med* **15** 487, 1928
- 2 Etiology, *ibid* **15** 495, 1928
- 3 Pulmonary Stenosis, *ibid* **15** 507, 1928
- 4 Coarctation of the Aorta, *ibid* **15** 521, 1928
- 5 Capillary Studies (with Dr Redisch), *ibid* **16** 463, 1929

- 6 Heart Dilatation in Congenital Arteriovenous Communication, *Klin Wchnschr* **8** 1621, 1929
- 7 Isolated Dextrocardia (monograph), *Wien Arch f inn Med* **19** 505, 1930
- 8 Interatrial Septal Defect with Mitral Stenosis (with Dr Dressler), *Ztschr f klin Med* **112** 421, 1930
- 9 Electrocardiographic Studies (with Dr Kiss), *Wien Arch f inn Med* **21** 271, 1931
- 10 Studies in Heredity (with Dr Medvei), *Ztschr f klin Med* **119** 527, 1932

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EFFECT OF TOXEMIA ON THE TOLERANCE FOR DEXTROSE AND ON THE ACTION OF INSULIN II

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The experiments presented in this paper are a continuation of observations bearing the same title and published at an earlier date in the ARCHIVES¹ It has been shown in previous studies² that diphtheria toxin produces a toxemia in rabbits which lessens the animals' ability to remove dextrose from the blood as judged by the dextrose tolerance test In animals poisoned with diphtheria toxin, after several days of toxemia, the blood sugar two hours after the administration of 5 Gm of dextrose was found to range as high as 400 and 500 mg per hundred cubic centimeters Small uniform doses of insulin were then administered, and it was originally thought that a constant and uniform effect of the insulin could be noted as the toxemia increased In our earlier study,¹ daily increased doses of insulin were injected twenty minutes prior to the administration by stomach tube of a constant quantity of 5 Gm of dextrose Prior to the last series of experiments, it was thought that the effect of the toxemia in question was largely that of a suppression of endogenous insulin It was found, however, that the toxic rabbits tolerated doses of insulin as large as 12 and 14 units injected twenty minutes before 5 Gm of dextrose was given The tolerance curves remained practically normal in all of the toxic animals that received these doses of insulin best Since it required such large doses of insulin to maintain normal curves following these relatively

1 Sweeney, J S , Barshop, N , and LoBello, L C Effect of Toxemia on Tolerance for Dextrose and on the Action of Insulin I, Arch Int Med **53** 689 (May) 1934

2 Sweeney, J S , and Lackey, R W The Effect of Toxemia on Tolerance for Dextrose, Arch Int Med **41** 257 (Feb) 1928 Sweeney, J S Effect of Toxemia on Tolerance for Dextrose and on the Action of Insulin, *ibid* **41** 420 (March) 1928

small amounts of dextrose, we were compelled to conclude that the toxemia in some way interfered with the function of insulin whether it was endogenous or exogenous in origin

In order to lend confirmation to this explanation of the effect of this type of toxemia on the tolerance for dextrose and the action of insulin,

TABLE 1—Results of Daily Tests of the Tolerance for Dextrose of Rabbit A*

Observation, Hours	Insulin, Units	Dextrose, Gm	Blood Sugar, Mg per 100 Cc			
			Fasting	After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
0	0	5	69	108	154	116
24	2	5	74	98	105	104
48	4	10	69	118	182	133
72	6	15	74	100	105	105
96	8	20	76	100	105	91
120	10	25	83	103	111	105
144	12	30	85	168	221	89

* This animal received no toxin, but was given daily increased quantities of insulin and dextrose in a ratio of 1 unit of insulin to 2.5 Gm of dextrose

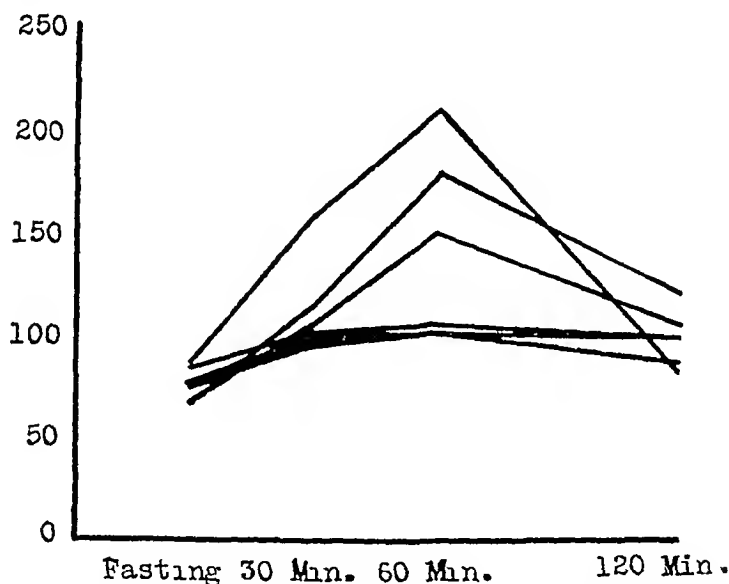


Chart 1—Daily curves showing the tolerance for dextrose of rabbit A. No toxin was given to this animal (table 1). Daily increased quantities of insulin and dextrose were given in a ratio of 1 unit of insulin to 2.5 Gm of dextrose.

the following experiments were undertaken. Rabbits were intoxicated with 0.0025 cc of diphtheria toxin (minimal lethal dose, 0.02 cc), which was found to be an optimal dose, i.e., one that killed the rabbits within from five to seven days. Dextrose tolerance tests were made on the animals daily. Instead of giving a constant dose of dextrose, how-

TABLE 2—Results of Daily Tests of the Tolerance for Dextrose of Rabbit 7 *

Starvation, Hours	Toxemia, Hours	Dextrose, Gm	Blood Sugar, Mg per 100 Cc			
			Fasting	After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
21		5	105	182	179	145
48	24	5	107	152	206	206
72	48	5	95	174	230	333
96	72	5	100	190	244	345
120	96	5	109	190	296	357
144	120	5	120	215	313	400

* This animal was given a subcutaneous injection of 0.0075 cc of diphtheria toxin (minimal lethal dose, 0.03 cc) Five grams of dextrose was given daily

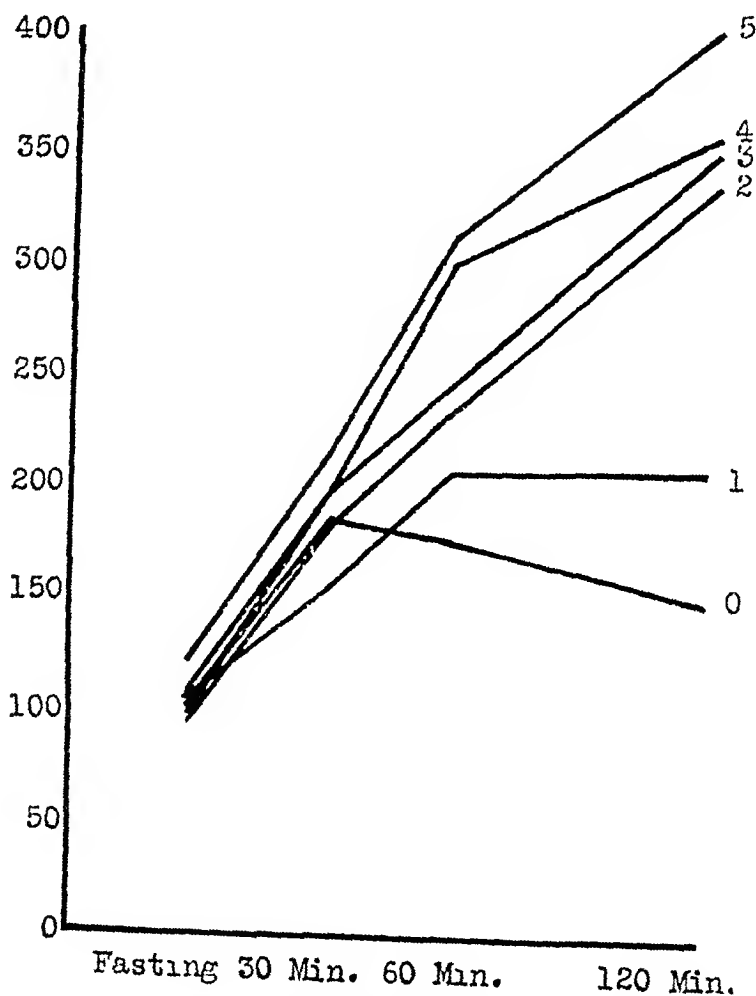


Chart 2—Daily curves showing the tolerance for dextrose of rabbit 7 Toxin was not given The numbers at the end of each curve indicate the day of starvation Five grams of dextrose was given each day

ever, we gave increasing doses each day. Insulin was given subcutaneously twenty minutes before each test in the doses used in the previously mentioned experiments, namely, daily 2 unit increments, and dextrose was given in quantities that are theoretically cared for by this quantity of insulin, i. e., a ratio of 1 unit for each 2.5 Gm of dextrose.

TABLE 3—Results of Daily Tests of the Tolerance for Dextrose of Rabbit G*

Toxemia, Hours	Insulin, Units	Dextrose, Gm	Blood Sugar, Mg per 100 Cc			
			Fasting	After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
0	0	5	83	143	165	109
24	2	5	87	138	125	103
48	4	5	89	125	85	70
72	6	5	100	111	95	80
96	8	5	84	129	129	118
120	10	5	100	133	120	105
144	12	5	111	140	132	111

* This animal was given 0.005 cc of diphtheria toxin (minimal lethal dose, 0.02 cc). Increased doses of insulin were injected each day twenty minutes before 5 Gm of dextrose was given.

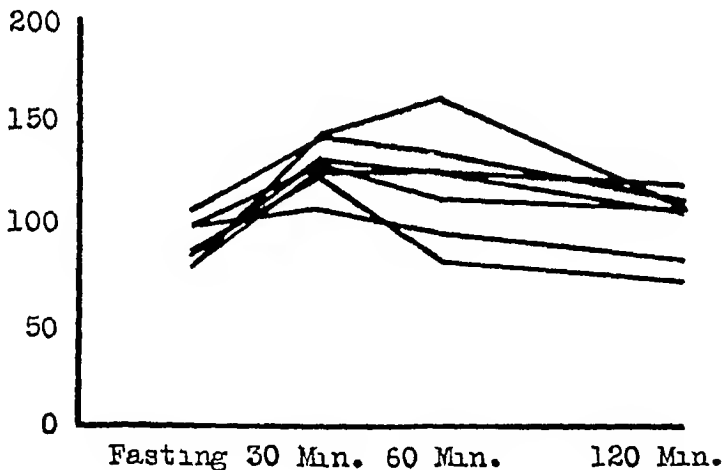


Chart 3—Daily curves showing the tolerance for dextrose of rabbit G. The animal received 0.005 cc of diphtheria toxin. Daily increased doses of insulin were injected twenty minutes before 5 Gm of dextrose was given (table 3).

In table 1 and chart 1 are the figures and curves, respectively, for the control rabbit. This animal received no toxin but was given dextrose in quantities of from 5 to 30 Gm and insulin in doses of from 2 to 12 units. It will be noted that all of the curves are practically normal, with the exception of one on the seventh day, which had a marked rise but fell within two hours to a level of 89 mg per hundred cubic centimeters. For the purpose of comparison, tables 2 and 3 and

TABLE 4—Results of Daily Tests of the Tolerance for Dextrose of Rabbit B*

Toxemia, Hours	Insulin, Units	Dextrose, Gm	Blood Sugar, Mg per 100 Cc			
			Fasting	After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
0	0	5	78	105	125	95
24	2	5	111	125	111	100
48	4	10	91	100	100	91
72	6	15	95	267	264	200
96	8	20	100	200	250	222

* This animal was given a subcutaneous injection of 0.0025 cc of diphtheria toxin (minimal lethal dose, 0.02 cc). Daily increased quantities of insulin and dextrose were given in a ratio of 1 unit of insulin to 2.5 Gm of dextrose.

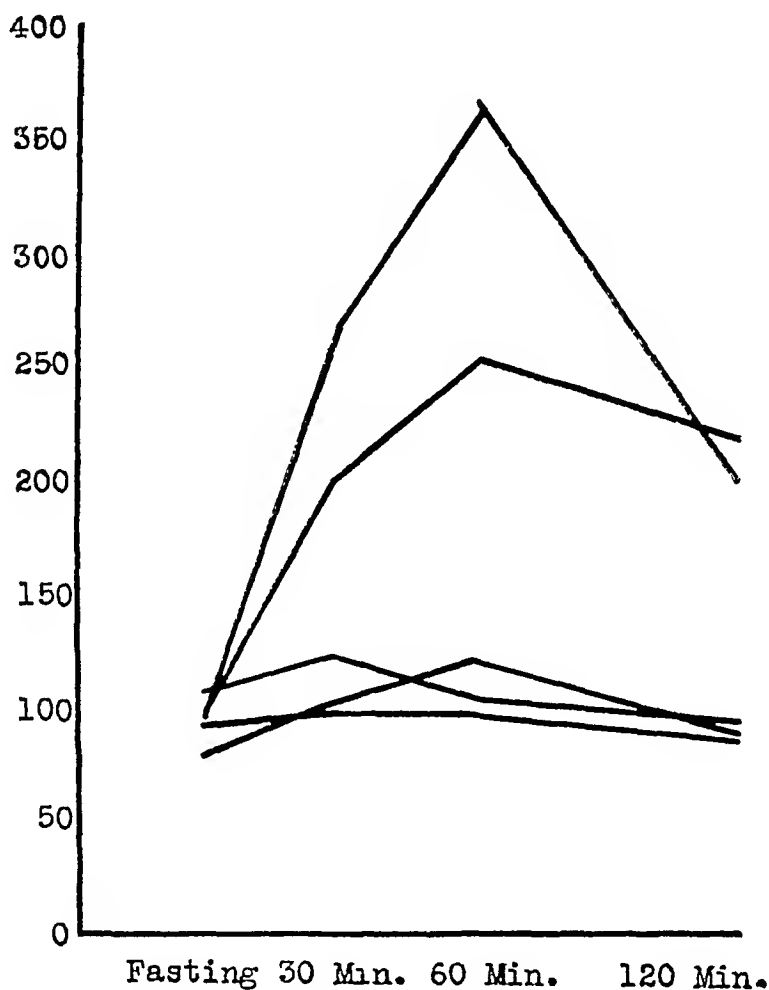


Chart 4—Daily curves showing the tolerance for dextrose of rabbit B. Daily increased quantities of insulin and dextrose were given in a ratio of 1 unit of insulin to 2.5 Gm of dextrose.

TABLE 5—Results of Daily Tests of the Tolerance for Dextrose of Rabbit C*

Toxemia, Hours	Insulin, Units	Dextrose, Gm	Blood Sugar, Mg per 100 Ce			
			Fasting	After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
0	0	5	70	121	154	117
24	2	5	70	98	125	148
48	4	10	100	167	211	250
72	6	15	98	200	267	348
96	8	20	80	222	400	Dead

* This animal was given a subcutaneous injection of 0.0025 cc of diphtheria toxin (minimal lethal dose, 0.02 cc) Daily increased quantities of insulin and dextrose were given in a ratio of 1 unit of insulin to 2.5 Gm of dextrose

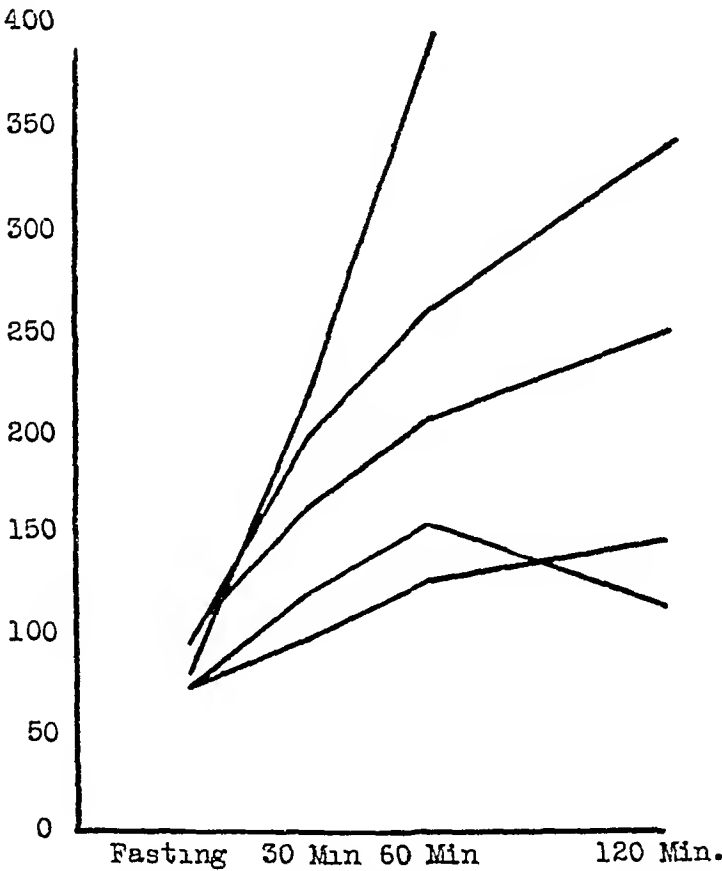


Chart 5—Daily curves showing the tolerance for dextrose of rabbit C Daily increased quantities of insulin and dextrose were given in a ratio of 1 unit of insulin to 2.5 Gm of dextrose

charts 2 and 3 are reproduced from the previous studies In table 2 and chart 2 are the figures for a toxic animal that received only 5 Gm of dextrose daily during the period of toxemia but received no insulin

TABLE 6—Results of Daily Tests of the Tolerance for Dextrose of Rabbit D*

Toxemia, Hours	Insulin, Units	Dextrose, Gm	Blood Sugar, Mg per 100 Cc			
			Fasting	After Dextrose		
				30 Minutes	60 Minutes	120 Minutes
0	0	5	85	154	160	127
24	2	5	80	143	133	91
48	4	10	111	182	222	222
72	6	15	95	182	235	222
96	8	20	83	143	200	222
120	10	25	110	202	267	Dead

* This animal was given a subcutaneous injection of 0.0025 cc of diphtheria toxin (minimal lethal dose, 0.02 cc) Daily increased quantities of insulin and dextrose were given in a ratio of 1 unit of insulin to 2.5 Gm of dextrose

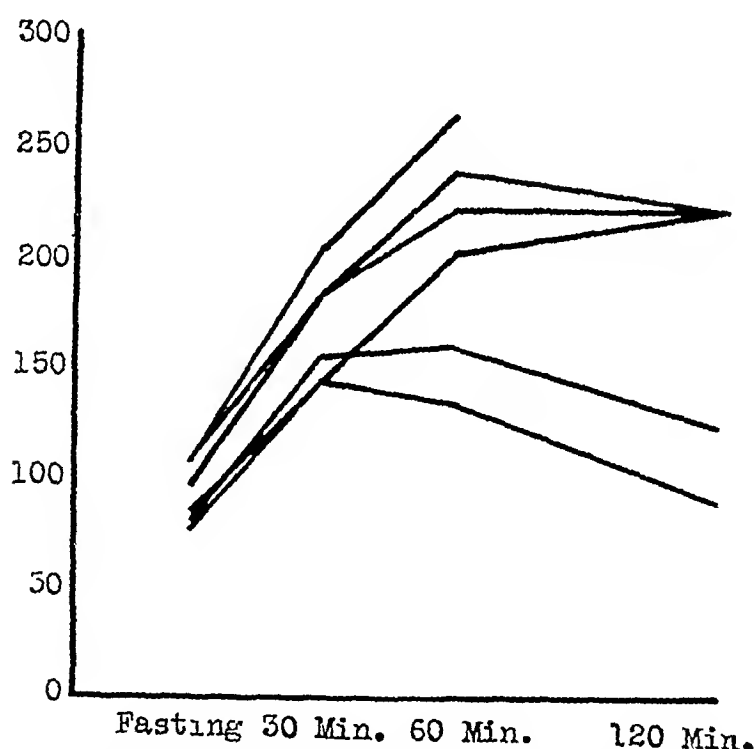


Chart 6—Daily curves showing the tolerance for dextrose of rabbit D Daily increased quantities of insulin and dextrose were given in a ratio of 1 unit of insulin to 2.5 Gm of dextrose

In table 3 and chart 3 are the figures for a toxic animal that received daily 2 unit increments of insulin injected twenty minutes before a constant quantity of 5 Gm of dextrose was given

In tables 4, 5 and 6 and charts 4, 5 and 6 are the figures for three toxic animals that received daily increased doses of insulin and dextrose

As the toxemia increased, the tolerance curves became more and more abnormal. In contrast to the results obtained in the nontoxic rabbits, the theoretical dose of insulin necessary to dispose of the increasing quantities of dextrose was inadequate in the toxic rabbits.

CONCLUSION

These findings definitely confirm the conclusions reached in our previous experiments. What the mechanism is whereby the action of exogenous insulin is inhibited by the toxemia in question is not clear. It may be a neutralization phenomenon or the toxemia may inhibit glycogenesis or oxidation. Further studies are in progress from which it is hoped a more specific explanation may be offered. From these observations, it at least seems conclusive that the effect of this type of toxemia is not just that of a suppression of endogenous insulin, as previously thought. Its effect seems clearly that of an interference with the function or action of insulin, whether the insulin is of endogenous or exogenous origin.

Medical Arts Building

SIGNIFICANCE OF THE INORGANIC SULPHATE CLEARANCE IN RENAL DISEASE

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It is not the intention here to add another somewhat complicated procedure to the already rather formidable list of tests of renal function. However, on the basis of the work of Wakefield, Power and Keith,¹ confirmed by Hayman and Johnston,² showing that the concentration of inorganic sulphate in the blood is often elevated before the urea, the sulphate clearance should show a change before the urea clearance and should give still earlier evidence of impaired renal function. Here, of course, is met the question of renal physiology. How is inorganic sulphate eliminated by the kidney? In what way does its excretion differ from that of urea or creatinine? Certain valuable and useful laws governing the excretion of urea, leading to the urea clearance test, have been established without knowledge of the exact histologic mechanism by which it takes place, and the same may be true for sulphate.

One of the difficulties of working in the metabolism of sulphur has been that of finding a satisfactory method for making determinations. Survey of the methods which various investigators have used will not be included here. Power and Wakefield³ recently perfected the volumetric method, which is now being used as a routine at the Mayo Clinic, and this method was used in all of the determinations of serum and urine reported in this paper.

The work presented here consists of a series of simultaneous urea and sulphate clearances determined for normal subjects and for patients

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1 Wakefield, E. G., Power, M. H., and Keith, N. M. Inorganic Sulphates in the Serum in Early Renal Insufficiency, Significance of Determinations, *J. A. M. A.* **97** 913 (Sept. 26) 1931

2 Hayman, J. M. Jr., and Johnston, Sara M. The Excretion of Inorganic Sulphate, *J. Clin. Investigation* **11** 607 (May) 1932

3 Power, M. H., and Wakefield, E. G. A Method for the Determination of Inorganic Sulphate in Blood Serum, *Proc. Staff Meet., Mayo Clin.* **6** 401 (July 8) 1931

with definite or suspected renal disease. The normal subjects were all male except one and were members of the permanent staff of the Mayo Clinic and the Mayo Foundation or of the fellowship staff of the Mayo Foundation. All of the patients were in the hospital service of Dr. N. M. Keith.⁴ The conditions of the test were as nearly standard as possible. All of the normal subjects had the diet to which they were accustomed, and no attempt was made to calculate the various constituents. The patients had various so-called nephritic diets of which the content of protein and the caloric value were known. Most of the experiments were done in the morning, following breakfast, at which coffee was eliminated because Addis and Drury⁵ showed that coffee affected the clearance of urea. A few experiments were carried out after the noonday lunch. No particular attempt was made to regulate the intake of fluid, although the aim was that the range of volume of urine passed by normal subjects should be wide. All of the normal subjects were at rest, as were most of the patients, or were engaged in the usual professional work around the clinic, so there was no marked physical activity in any instance.

The bladder was emptied as soon after the meal as was convenient, and one hour after the emptying of the bladder a specimen of urine was collected, care being taken to save all of the urine. The volume was measured, and determinations of sulphate and urea were made on the specimen. Blood was drawn from the median basilic vein about ten minutes before the end of the hour and the same determinations were made, serum being used for the estimation of sulphate and whole blood for the estimation of urea. In a number of instances the determination was made for two consecutive hours. Determinations of urea were made by Marshall's method as modified by Van Slyke and Cullen.⁶ All of the work on serum sulphate was done in the same laboratory as that in which the original work of Wakefield, Power and Keith¹ was done. Most of the estimations of urine sulphate were made in duplicate, and if the difference was more than could be explained by experimental error, the results were discarded and the test repeated. All of the values for sulphate in this report are expressed as SO_4 , expressed as S, the value would be one third as much.

In four normal subjects during the experiment, the creatinine ratio (the concentration of creatinine in the urine divided by the concentration of creatinine in the blood) and the creatinine clearance were

4 Keith, N. M. Personal communication to the author.

5 Addis, T., and Drury, D. R. The Rate of Urea Excretion. VII. The Effect of Various Other Factors than Blood Urea Concentration on the Rate of Urea Excretion, *J. Biol. Chem.* **55** 629 (April) 1923.

6 Van Slyke, D. D., and Cullen, G. E. A Permanent Preparation of Urease, and Its Use in the Determination of Urea, *J. Biol. Chem.* **19** 211, 1914.

estimated when the values for urea and sulphate were determined. The conditions were essentially the same, except that, in the work with creatinine, 5 Gm of creatinine was taken by mouth at 7 a. m. The bladder was emptied at 8 a. m., and after one hour a specimen of urine was collected. Blood was drawn, and the determinations of creatinine were made with the determinations of urea and sulphate. The method of Folin⁷ was used for the estimation of creatinine in the urine, and a similar method, described by the same author,⁸ for the creatinine in the blood. Again, in some cases the test was run for two consecutive hours.

In addition, in one normal subject the effect of diet on the excretion of sulphate was determined. The subject voided at 8 a. m., and the urine was collected at 10 a. m., 12 noon, 3, 6, 9 and 11 p. m. and again at 8 a. m., and the sulphate in each specimen was measured. This was done on two different days, with a diet of approximately 2,500 calories, containing 75 Gm of protein. The same procedure was carried out on two occasions while the subject was on a starvation regimen. In the latter case, no food was taken for thirty-six hours, and specimens of urine were collected at the same times as those mentioned at the beginning of the paragraph. The first collection, that at 10 a. m., was sixteen hours after the beginning of the fast. On one day, under each of the conditions described, determinations of serum sulphate were made at varying periods.

EXPERIMENTAL RESULTS

The excretion of sulphate over a period of twenty-four hours, under conditions of normal diet and of fasting, will be given first to emphasize the importance of regulating this factor whenever work is being done in this field (table 1). On the first day, only one specimen was taken between 8 and 12 a. m., which explains the duplication of figures in the first two columns. It was seen that when the subject was taking the usual amount of food, the rate of excretion was lowest during the morning hours and then gradually rose, reaching a peak on both days between 6 and 9 p. m., with the excretion at night relatively low. When food was not taken, on the other hand, the rate of excretion was fairly constant during the day, with some increase at night, and at all times was much lower than when the subject was receiving a full diet. The total output of inorganic sulphate (SO_4) on the two days when the intake of food was normal was 2.205 Gm and 2.331 Gm, respectively, on the days when food was not ingested, 1.092 and 1.062 Gm. Kahn

7 Folin, Otto. On the Determination of Creatinine and Creatine in the Urine, *J. Biol. Chem.* **17** 469, 1914.

8 Folin, Otto. *Laboratory Manual of Biological Chemistry*, ed. 3, New York, D. Appleton and Company, 1922, p. 245.

and Goodridge⁹ found 2.35 Gm of inorganic sulphate (expressed as SO_3) in a twenty-four hour specimen of urine of a human being and wrote that the output at varying times of the day, "varies with personal idiosyncrasy, various conditions of life, and the time of taking the chief meal" In his study of a professional faster, Benedict¹⁰ found the excretion in twenty-four hours to be 0.46 Gm of total sulphur on the first day of the fast, and it remained at almost this level—0.50 Gm on the fifteenth day and 0.52 Gm on the thirtieth day He quoted two other authors, also working with professional fasters, who gave 0.62 and 0.614 Gm of total sulphur, respectively, as the output in twenty-four hours on the first day of fasting He did not state what portion of the total sulphur was present as inorganic sulphate Osterberg and Wolf¹¹ divided the day's output of urine into two twelve hour specimens, one collected while the subject was at rest and one while he was

TABLE 1—*The Effect of Diet on the Average Excretion of Inorganic Sulphate in the Urine of a Normal Subject**

Diet	Time						
	8 to 10 A M	10 A M to 12 M	12 M to 3 P M	3 to 6 P M	6 to 9 P M	9 to 11 P M	11 P M to 8 A M
	Mg per Hour						
Normal	55.0	55.0	80.1	117.4	132.9	128.5	86.4
Normal	75.8	99.3	103.6	112.5	123.7	121.1	83.4
Fasting	49.0	37.5	34.8	42.5	42.0	43.2	57.5
Fasting	36.6	40.3	47.3	31.2	41.2	48.1	55.2

* This is subject 2 of table 2

moderately active, they found that the output was larger when the subject was moderately active than when he was at rest

The values for serum sulphate varied much less When the intake of food was normal, the range of four determinations was only from 4.8 mg in each 100 cc of serum to 5.33 mg in each 100 cc, with the highest value for serum sulphate corresponding to the period of greatest elimination of inorganic sulphates On the day of fasting, three values for serum sulphate were 4.1, 4.6 and 4.7 mg in each 100 cc It is obvious, therefore, that clearance values taken at corresponding periods of the day under the two conditions or at different periods of the day when the patient is receiving a normal diet may vary widely

In table 2 are given the concentrations of sulphate and urea in the blood and the urine, the sulphate and urea ratios (the concentration in

⁹ Kahn, Max, and Goodridge, F G Sulfur Metabolism, Philadelphia, Lea & Febiger, 1926, p 136

¹⁰ Benedict, F G A Study of Prolonged Fasting, Washington, D C, Carnegie Institution, 1915, publ 203, p 277

¹¹ Osterberg, E, and Wolf, C G L Day and Night Urines, J Biol Chem 3 165, 1907

the urine divided by the concentration in the blood) and the sulphate and urea "clearances" in a group of normal subjects. All of the sulphate clearances were determined by the formula $\frac{U}{S} \times v$ in which U represents the concentration in the urine, S the concentration of sulphate in the serum and v the volume of urine per minute. The formula gives,

TABLE 2—*Concentration Ratios and Clearance of Sulphate and Urea in Normal Subjects*

Sub ject	Urine, Cc per Minute	Serum Sul phate, Mg per 100 Cc	Urine Sul phate, Mg per 100 Cc	Sul phate Ratio	Blood Urea, Mg per 100 Cc	Urine Urea, Mg per 100 Cc	Urea Ratio	Clearance		
								Sulphate $\frac{U}{S} \times V^*$	Urea $\frac{U}{B} \times V^*$	Urea $\frac{U}{B} \times \sqrt{V^*}$
1	0.25	4.7	264	56	30	3,495	117	14	29	58
2	0.43	4.4	222	51	26	2,211	85	22	37	52
2	0.5	4.7	227	48	30	2,185	73	24	36	60
2	0.53	3.9	256	65	20	1,464	73	34	39	52
3	0.58	4.7	285	61	27	3,026	112	34	67	87
3	0.58	5.2	283	55	30	2,547	85	32	51	66
4	0.6	4.5	232	52	28	2,420	86	30	52	66
5	0.8	5.1	240	47	30	1,460	49	39	37	42
5	0.83	5.8	257	44	23	1,399	54	35	45	48
5	1.0	4.2	81	19	28	1,194	43	19	43	43
2	1.0	4.2	125	30	22	1,300	60	30	57	57
2	1.0	4.1	120	29	20	1,330	67	29	66	66
6	1.0	4.5	152	34	26	1,726	66	34	66	66
2	1.1	4.2	113	27	24	1,293	54	29	59	55
4	1.2	5.1	180	35	30	1,850	62	41	74	68
7	1.25	4.4	125	28	30	1,285	43	35	54	48
2	1.27	4.4	104	24	24	1,246	52	30	66	59
2	1.3	4.5	81	18	33	1,192	36	24	47	42
2	1.3	4.0	96	24	18	986	55	41	71	62
2	1.42	4.4	102	23	20	1,363	68	33	97	82
8	1.55	3.5	75	22	25	918	35	33	55	43
9	1.58	3.4	89	26	24	1,118	47	41	75	59
2	1.95	4.4	79	18				35		
2	2.0	4.2	50	12	21	768	28	24	40	
7	2.0	4.4	81	18	28	950	38	37	48	
1	2.25	4.3	57	14	40	731	18	30	41	
9	2.58	3.4	48	14	22	632	29	39	75	
6	2.78	4.3	55	13	22	562	26	36	71	
10	2.8	4.4	116	26	26	1,318	51	74	168	
11	2.83	3.9	43	11	14	422	30	31	84	
12	3.0	4.2	48	12	16	551	34	35	103	
7	4.66	4.7	44	9	24	421	18	44	82	
12	5.6	4.1	29	7	14	246	18	40	98	
2	6.0	4.4	27	6	14	294	21	36	126	
8	6.83	3.5	21	6	24	325	14	37	83	
11	9.33	4.8	16	3	18	180	10	30	93	
2	10.17	4.4	19	4	30	207	7	44	70	
2	11.83	4.4	17	4	20	170	9	46	100	

* This is explained in the text

in theory, the actual number of cubic centimeters of blood cleared of sulphate in one minute. The same result would be obtained by determining the number of milligrams of sulphate eliminated in the urine in one minute and dividing this by the amount contained in 1 cc of serum, one would thus find the volume of blood which would contain the amount of sulphate eliminated in this period of time. Nothing, therefore, is taken for granted in using this formula, for it represents the simplest possible ratio if these three factors are to be taken into consideration. Moreover, since the concentration of sulphate in the serum of a normal

person varies within narrow limits, and since, as will be shown later, the output is to a large measure independent of the volume of urine, there was no indication that the formula should be modified. In the first column of figures, recording urea clearance, the same method was used to obtain the results, B represents the concentration of urea in the blood. In the second column, the formula $\frac{U}{B} \times v$ was used for cases in which the volume of urine was less than 2 cc each minute.

These results are evidence, first, that the sulphate ratio is lower than that of the urea, although in one or two instances the ratios closely approached each other, and in an occasional case, not shown in table 2 the sulphate ratio was higher. The range for sulphate is from 3 to 65, and that for urea from 7 to 117. Second, the results indicate that there is a greater uniformity of sulphate clearance than of urea clearance. This is not so much in evidence if only the extreme instances are considered, for the sulphate clearance ranges from 14 to 74, and the urea clearance from 29 to 168, if a similar formula is used. When the formula $\frac{U}{B} \times v$ is used for a volume of urine of less than 2 cc per minute, the urea clearance varies from 42 to 87. However, a larger number of values for sulphate than for urea fall within the average. This factor will be illustrated again in tables 3 and 4. Third, the results constitute evidence that the sulphate clearance is relatively unaffected by the volume of urine, although the latter exerts a slight influence as will be shown later. The impression to be gained is that the excretion of sulphate must differ from that of the urea, because the volume of urine in the former case plays a less important part, and in measuring sulphate clearance, for all practical purposes, no "augmentation limit" need be considered.

In most respects the results were similar to those of Hayman and Johnston² and Cope,¹² who found with few exceptions that the concentration ratio of sulphate was lower than that of urea. Hayman and Johnston, however, had somewhat less uniformity in their figures for the sulphate ratio and concluded that the laws of excretion of sulphate are similar to those for excretion of urea as given by Moller, McIntosh and Van Slyke,¹³ so far as the volume of urine is concerned and that the augmentation limit is at about the same level, namely, between 1 and 2 cc for one minute. Cope's figures for sulphate clearance, on the other hand, are even more constant than those given here and correspond closely to them. He, too, found that the volume of urine has little effect on the result.

12 Cope, C. L. Inorganic Sulphate Excretion by the Human Kidney, *J. Physiol.* **76** 329 (Nov.) 1932.

13 Moller, Eggert, McIntosh, J. F., and Van Slyke, D. D. Studies on Urea Excretion. II. Relationship Between Urine Volume and Rate of Urea Excretion by Normal Adults, *J. Clin. Investigation* **6** 427 (Dec.) 1928.

In attempting to determine from table 2 a normal value for sulphate clearance, it was found that twenty-six of thirty-eight determinations (68 per cent) lay between 25 and 40, with six falling on either side of this range. Only two were below 20. One of these was 19, and this subject had two other values, 39 and 35, respectively. The other was 14, and the volume of urine, when this was obtained, was only 0.25 cc each minute, with a larger urinary output, the clearance of this person was 30. It may be deduced from these results that low volumes of urine affect the output of inorganic sulphate, and in order to obtain normal clearance the volume should be 0.5 cc or more each minute. From these figures it seems justifiable to take 20 as the lower limit of normal if the output of urine equals, or exceeds, the minimal amount. It seems conservative to take 20 as the lower limit, since 34 is found

TABLE 3—*Comparison of Sulphate, Urea and Creatinine Clearances, Normal Subjects*

Subject*	Sulphate	Urea	Creatinine
	$\frac{U}{S} \times V$	$\frac{U}{B} \times V$	$\frac{U}{B} \times V$
8	58	63	190
8	57	38	171
13	30	34	158
13	33	58	144
3	49	49	217
3	46	48	185
2	30	70	217
2	28	60	178
2	30	66	356
2	24	40	185

* Subjects 8, 3 and 2 are represented also in table 2

to be the average of all of the normal values in this series, and since Cope also reported an average in normal subjects which is close to this figure. In two groups his average was 35.6 and 35.3, respectively, whereas in eleven determinations made on the same subject the average clearance was 32.1.

Table 3 gives a comparison of sulphate, urea and creatinine clearance, determined simultaneously on normal subjects. The two series of values recorded for the first three subjects represent tests made during two consecutive hours, whereas the results representing subject 2 were obtained on four different occasions. These figures confirm the observations of Hayman and Johnston² and Cope¹² that the clearance of sulphate, or in other words, the concentration of sulphate by the kidney, is less than that of the urea in most instances, and that both of these substances are concentrated to a much smaller degree than is creatinine. They also indicate again that the sulphate clearance tends to be more constant than that of either the urea or the creatinine. This is best illustrated in subject 2, whose range for sulphate clearance is only

from 24 to 30 for urea from 40 to 70 and for creatinine from 178 to 356

In table 4 are given the hourly output in milligrams of inorganic sulphate and the clearance values for sulphate and urea as obtained for one normal subject on fifteen different occasions, with varying degrees of diuresis. This indicates that the volume of urine may play some part in the excretion of sulphate, in that the lowest output was obtained with the lowest volume and the greatest output with the maximal volume. However, it is seen that for outputs of urine of from 0.5 to 6 cc each minute, little effect is apparent, and it is only at the extremes that this factor assumes any importance. Table 4 again indicates that the constancy of sulphate is greater than that of the corresponding urea clearances.

TABLE 4—*Hourly Output of Sulphate, Sulphate Clearance and Urea Clearance, with Varying Degrees of Diuresis One Normal Subject**

Urine per Minute, Cc	Output of Sulphate, Mg per Hour	$\frac{U}{S} \times V$	$\frac{U}{B} \times V$
0.43	58	22	37
0.5	61	24	36
0.53	82	34	39
1.0	75	29	57
1.0	72	30	66
1.1	73	29	59
1.2	75	30	66
1.3	79	31	47
1.3	65	24	71
1.42	87	33	97
1.95	92	35	
2.0	61	24	40
6.0	95	36	126
10.2	119	44	70
11.8	122	46	100

* This is subject 2 of table 2

Table 5 gives data similar to those given in table 2, but the persons represented in table 5 had real or suspected renal disease. In only one case was the disease advanced. Again, except in two cases, the urea ratio exceeded that of the sulphate. One of the patients gave little evidence of renal injury, the other patient was in the terminal stages of uremia. In general, there seems to be a tendency for these ratios to approach each other as renal function becomes more seriously impaired. This is in accord with the observations of Cuthbertson and Tompsett,¹⁴ who stated "Relative to nitrogen, inorganic sulphate is retained in proportionally greater amount in minor degrees of retention than in more severe types, where relative to nitrogen it is less prominent."

¹⁴ Cuthbertson, D. P., and Tompsett, S. L. Preliminary Note on the Inorganic Sulphate Content of the Blood with a Method for Its Determination, *Biochem J* 25 1237 (July-Aug.) 1931

In table 6 is given a summary of the renal status of a group of patients with definite or suspected disease of the kidney, including data on most of those listed in table 5. The results of the tests commonly employed at the Mayo Clinic and the sulphate clearance in each case are given. As has been stated, 20 cc each minute has been taken as the lower limit of normal for the sulphate clearance. For serum sulphate, anything more than 5.5 mg for each 100 cc of serum is considered to be abnormal,

TABLE 5—*Sulphate and Urea Ratios and Clearance of Sulphate and Urea, Patients with Some Evidence of Renal Disease*

Sub ject	Urine, Cc per Minute	Serum Sul phate, Mg per 100 Cc	Urine Sul phate, Mg per 100 Cc	Sul phate Ratio	Blood Urea, Mg per 100 Cc	Urine Urea, Mg per 100 Cc	Urea Ratio	Clearance		
								Sulphate $\frac{U}{S} \times V$	Urea $\frac{U}{B} \times V$	Urea $\frac{U}{B} \times \sqrt{V}$
14	0.42	4.3	207	48	33	2,055	62	20	26	39
15	0.42	3.2	193	37	36	1,354	38	16	16	24
16	0.42	9.2	87	9	24	1,049	44	4	18	28
17	0.43	5.7	153	27	26	2,049	79	11	34	50
18	0.47	4.1	173	42	16	1,657	104	16	48	74
14	0.5	4.3	224	72	40	1,956	49	26	25	35
19	0.5	7.8	54	7	36	811	23	3	11	16
20	0.6	5.6	168	30	26	1,570	60	18	36	47
20	0.6	5.9	140	24	36	1,504	42	14	25	33
21	0.67	4.6	91	20	16	1,330	83	13	56	68
18	0.7	4.3	106	25				17		
22	0.7	4.8	291	61	32	2,215	69	42	48	58
23	0.7	6.7	31	5	36	515	14	3	10	12
22	0.73	5.1	287	57	28	2,299	82	43	60	71
15	0.75	5.2	168	31	40	1,618	40	24	30	35
24	0.75	11.7	90	8				6		
24	0.78	11.5	86	7	124	632	4	6	4	5
25	0.83	5.2	62	12	30	719	24	10	20	22
16	0.92	9.2	61	7	20	856	43	6	39	41
17	0.92	5.7	123	22	20	1,678	84	20	77	80
19	0.92	7.2	68	9	36	815	23	9	21	22
26	0.92	7.5	86	11	55	951	17	11	16	17
21	1.08	4.6	65	14	16	975	61	15	66	64
27	1.28	5.2	96	19	34	1,246	37	24	47	42
23	1.47	6.7	25	4	36	402	11	6	16	13
28	1.75	4.9	37	8	18	548	31	13	53	40
25	2.66	5.7	30	5	20	288	14	14	39	
26	2.83	7.6	27	4	58	367	6	10	16	
27	3.25	5.2	63	12	34	845	25	39	81	
29	3.66	6.2	27	4	38	400	11	16	39	
29	4.58	6.2	21	3	38	347	9	15	42	
28	5.0	5.1	17.2	3				17		
30	5.17	3.8	13.2	4	22	151	7	19	35	
30	5.25	3.7	29	8	22	424	19	40	101	

and for urea anything more than 40 mg for each 100 cc of blood. The lowest value considered normal for "standard" urea clearance (when the volume of urine is less than 2 cc each minute) is 40 cc, and for the "maximum" urea clearance 60 cc each minute. Excretion of phenol-sulphonphthalein by a normal subject for two hours after intravenous administration should be 50 per cent or more. Only in the cases indicated in the table was a concentration test performed. In other instances in which the specific gravity is given in the column in which the results of the concentration test are recorded the specific gravity recorded represents the highest figure that was obtained on routine examination of the urine, it is given in every case in which it was

TABLE 6.—Comparison of Sulphate Clearance with Other Studies of Renal Function, Patients with Evidence of Renal Injury

Subject	Age, Years	Sex	Serum Sulphate, Mg in 100 Cc	Urea in Whole Blood, Mg in 100 Cc	Creatinine, Mg in 100 Cc	Urea Clearance*	Sulphate Clearance	Hemoglobin, Gm in 100 Cc Blood	Retention of Phenolsulphon phthalein	Albumin, Grade	Erythrocytes, Grade	Casts, Grade	Dilution Test, Specific Gravity	Concentration Test, Specific Gravity	Blood Pressure, Mm of Mercury	Diastolic	Systolic	Retinitis	Ocular Fundl	Urine, per Minute	Diagnosis
31	32	F	5.8	22	1.1	65	44	14.2	80	1	0	0	1.002		165	90	0	0	0	4.5	Diffuse arterial disease with hypertension
22	38	M	5.2	24	1.3	71 s	43	16.4	80	1	0	0	1.004		118	80	0	0	0	0.7	Healed (?) glomerular nephritis
32	36	M	4.7	30	1.3	52 s	43	15.9	80	1	0	0	1.004		170	90	0	0	0	0.9	Diffuse arterial disease with hypertension
33	45	M	4.0	23	1.5	64 s	78	18.2	65	1	0	0	1.002	1.032†	165	115	1	0	0	1.1	Diffuse arterial disease with hypertension
34	56	M	4.7	23	1.3	74 s	34	16.7	55	2	0	0	1.004	1.025	160	100	1	0	0	0.8	Diffuse arterial disease with hypertension
35	41	F	4.9	24	1.3	55 m	33	13.3	45	2	0	0	1.004	1.028	170	100	0	0	0	2.9	Diffuse arterial disease with hypertension
36	53	F	4.6	24		64 s	33	12.7	70	0	0	0		1.026				0	0	1.3	Diffuse arterial disease with hypertension
37	50	F	3.8	30	1.2	59 s	32	14.2	60	1	0	0			150	90	0	0	0	0.8	Diffuse arterial disease with hypertension
38	56	F	4.9	32	1.3	43 s	31	17.2	50	2	0	0	1.002	1.028	190	100	1	0	0	1.2	Diffuse arterial disease with hypertension
39	53	F	2.9	30		48 s	28	15.7	65	1	0	0	1.002	1.026	135	80	0	0	0	0.7	Diffuse arterial disease with hypertension
40	74	M	4.7	24	1.3	57 s	28	17.2	50	0	0	0	1.003	1.025	170	70	1	0	0	1.0	Diffuse arterial disease with hypertension
41	45	M	6.5	22		75 s	26	14.2	50	1	1	1			125	70	0	0	0	1.7	Chronic glomerular nephritis
42	12	F	4.7	18	1.8	73 m	26	13.9	80	2	1	1	1.001	1.03†	110	76	0	0	0	2.3	Chronic glomerular nephritis, latent type
43	61	M	5.8	36	1.4	49 s	25	15.7	45	2	0	1	1.004	1.025	180	110	2	0	0	1.1	Diffuse arterial disease with hypertension
44	53	M	6.0	34		52 s	25	13.2	85	3	2	0	1.005	1.031	170	110	1	0	0	0.6	Diffuse arterial disease with hypertension
45	37	F	4.9	26	1.4	65 m	25	17.8	60	3	1	0	1.002		180	140	2	0	0	3.8	Diffuse arterial disease with hypertension
27	37	M	5.2	34	1.4	42 s	24	18.2	33	?	0	2	1.003		150	90	0	0	0	1.3	Chronic glomerular nephritis
46	43	M	4.3	32	1.5	51 m	23	14.4	60	2	0	0	1.002		200	120	2	2	2	4.1	Diffuse arterial disease with hypertension
47	57	M	5.6	18	1.3	69 m	22	11.4	40	4	0	2			85	50	0	0	0	1.8	Diffuse amyloidosis
48	50	F	3.0	20		35 s	22	15.2	60	2	0	0	1.003	1.027	200	120	0	0	0	0.6	Diffuse arterial disease with hypertension
49	50	M	9.0	98	5.4	30 m	22	13.1	5	3	2	0			210	130	?	?	?	3.7	Diffuse arterial disease with hypertension
50	51	M	5.5	36	1.4	35 s	21	13.3	50	2	0	0	1.005	1.028	180	110	1	0	0	0.5	Diffuse arterial disease with hypertension
14	62	M	5.0	40	1.4	39 m	20	18.2	45	0	0	0		1.025	190	110	0	0	0	0.5	Diffuse arterial disease with hypertension
51	29	M	4.0	24		54 s	19	15.7		0	0	0			126	76	0	0	0	0.9	History of previous acute glomerular nephritis
52	52	M	4.2	22	1.3	38 s	19	17.5	80	1	0	0	1.001		140	100	0	0	0	0.6	History of previous acute glomerular nephritis

1 025 or more, for it is evident in such cases that there could be no definite impairment of the concentrating ability. The result of the dilution test is given in each case in which it was performed. The normal subject should be able to produce urine of a specific gravity of 1 003 under the conditions of the test, but a number of factors may influence the result, and consequently a slightly higher figure is given consideration only in the presence of other evidence of impaired renal function.

The sulphate clearance in the first twenty-three cases recorded in table 6 was 20 or more and consequently within the accepted limits of normal. In twelve of the twenty-three cases all of the other tests were normal as well, whereas in eleven cases the results of one or more of the other tests were somewhat abnormal. In six of the latter group of eleven cases the value for serum sulphate was more than 5.5 mg. in each 100 cc. In cases 31, 41 and 44, this was the only evidence, so far as functional tests are concerned, of any impaired renal function, whereas in cases 43 and 47 the elevated value for serum sulphate was accompanied by a slightly reduced excretion of phenolsulphonphthalein. In case 49 there was unquestionable evidence of advanced renal insufficiency. In five of the eleven cases the urea clearance was low, and in cases 46 and 50 all of the other tests were within normal limits, whereas in cases 14 and 35, there was also some reduction in the output of phenolsulphonphthalein. Again, in case 49, the urea clearance was definitely lowered. The excretion of phenolsulphonphthalein was below 50 per cent in six instances, but in only one case (case 27) was this the only test in which the results were abnormal. In cases 14, 35, 43 and 47, there was also a change in the value for serum sulphate or that for urea clearance, and in case 49 all of the results were abnormal.

The finding of a normal sulphate clearance in the presence of an elevated value for serum sulphate such as that obtained in the six cases mentioned, in which the elevation was not due to an added ingestion on injection of sulphate, brings up a problem which is of importance and which deserves further study. Keith⁴ recorded a number of cases in which this was true for urea. Theoretically, the clearance should always be diminished under these circumstances, except perhaps during the stage of recovery from a condition which had brought about a period of elevation of the value for serum sulphate, during which this level was returning to normal. From the results obtained in the six cases mentioned, it must be admitted that the clearance of a substance is not always an infallible index as to its retention in, or elimination from, the organism.

Of the remaining thirty-five cases in which the sulphate clearance was less than 20, there were seven in which all of the other tests (except the dilution test) gave normal values. These were cases 18, 21, 28, 56,

59, 63 and 66 In four of these it is seen that the specific gravity of the urine after the dilution test did not reach 1.003 In two of the seven cases, the concentrating ability was not satisfactorily shown, for concentration tests were not made, and the highest specific gravity found on routine examination of the urine was 1.022 in both cases This is sufficient to show, however, that there could have been little, if any, impairment in this respect In the remaining five cases, the concentrating power was entirely satisfactory That the kidneys in these cases were definitely affected is indicated by the fact that all of the subjects had albuminuria, graded from 1 to 4, that erythrocytes were present in the urine in five of the seven cases, and that casts were found in four cases The diagnosis was "diffuse arterial disease with hypertension" in four of the seven cases, and "chronic glomerular nephritis," in the remaining three cases, in two of which there was a "nephrotic" element The most definite reduction of sulphate clearance was seen in the latter group, composed of cases 21, 28 and 66, in all of which there was a high grade of albuminuria with some edema This appears to be in keeping with the work of Grabfield,¹⁵ who found that the excretion of sulphur by patients with nephrosis was reduced, whereas the output of nitrogen was normal He attributed this not to any inability of the kidney to eliminate sulphur but to some defect in the intermediary metabolism of sulphur Among patients with "Bright's disease" but no edema, on the other hand, he¹⁶ found a negative sulphur balance No true experiments on sulphur balance have been carried out in this study or in the previous work dealing with serum sulphate, but so far as the inorganic sulphate is concerned, it apparently is retained in the presence of renal injury, regardless of the type of injury

The retention of sulphate and its slower return to normal in the serum and in the clearance value are illustrated in table 7 In the case on which this table is based acute renal insufficiency developed, which, however, responded readily to treatment Table 7 discloses that the value for the blood urea returned to normal before the value for the serum sulphate, and that the urea clearance was normal before the sulphate clearance, the sulphate clearance showing evidence of impaired function longer than any of the other tests, although it, too, was normal at the last determination Only one such case, perhaps, has little significance, but it is entirely in keeping with the seven cases considered earlier in the paper

15 Grabfield, G. P. Studies on the Nitrogen and Sulfur Metabolism in "Bright's Disease" I The Retention of Nitrogen and Sulphur in "Nephrosis," *J Clin Investigation* 9:311 (Oct) 1931

16 Grabfield, G. P. Studies on the Nitrogen and Sulfur Metabolism in "Bright's Disease" II Observations on Nitrogen and Sulphur Excretion in Patients Without Renal Edema, *J Clin Investigation* 10:309 (June) 1931

Therefore, of the fifty-eight patients listed in table 6, who were admitted to the hospital because of general clinical evidence or urinary changes which suggested renal disease, there were seven (approximately 12 per cent) whose only evidence of renal insufficiency, as far as functional tests were concerned, was reduced sulphate clearance. There were nine additional cases (cases 17, 52, 55, 57, 60, 62, 65, 67 and 68) in which the sulphate clearance was below normal, it was accompanied by an abnormal figure for only one other test, which in six of the nine cases was the urea clearance test. Of the total series of fifty-eight cases, there were forty-six in which one or more of the functional tests gave evidence of impaired renal function. The sulphate clearance was abnormal in 76 per cent of these forty-six cases, the urea clearance in 61 per cent, the value for serum sulphate in 52 per cent, the excretion of phenolsulphonphthalein in 39 per cent and the value for blood urea in 20 per cent.

TABLE 7—*Functional Tests During the Period of Recovery from Acute Renal Insufficiency*

	June 8	June 14	June 23	June 29
Blood urea, mg per 100 cc	93	40*	18*	16*
Serum sulphate, mg per 100 cc	9.4	6.0	4.7*	3.9*
Urea clearance†	14 (m)	21 (s)	45 (s)*	61 (m)*
Sulphate clearance	10	16	16	20*

* Normal

† Maximum clearance is indicated by (m), and standard clearance by (s)

COMMENT

Since the work of Rehberg,¹⁷ creatinine has been widely accepted as the "no threshold" substance par excellence, in spite of Rehberg's statement that the work was based on nothing more than a hypothesis as to the manner in which creatinine is eliminated by the kidneys. Many investigators have used it as a basis of comparison by which to determine the method of excretion of other metabolites. If a substance such as urea for instance is of lower ratio than the creatinine, it is taken as evidence of reabsorption of urea in the tubules. However the present figures give evidence of a constancy of output of inorganic sulphate which resembles that of creatinine as found by other workers. And this study, as well as those of Hayman and Johnston² and of Cope,¹² shows that under normal conditions the creatinine ratio is always much higher than that of the sulphate. The constancy of the output, in spite of considerable variation in the volume of the urine, seems to testify

17 Rehberg, P. B. Studies on Kidney Function. I. The Rate of Filtration and Reabsorption in the Human Kidney, *Biochem J* 20: 447 (May-June) 1926

against a tubular reabsorption of sulphate. But if the excretion is by the same mechanism as that of creatinine, ratios should be the same. Is this an argument in favor of the theory of a tubular secretion of creatinine? Cope suggested such a secretion as a distinct possibility, whereas Hayman and Johnston expressed the belief that the differences in ratio are best explained on the basis of a tubular reabsorption of sulphate. In this connection, the work of Shannon, Jolliffe and Smith¹⁸ is of interest, they have compared the excretion of creatinine with that of nonmetabolized sugars.

From the clinical point of view, further investigations must be made before the sulphate clearance can be assigned in its proper place among the tests of early renal insufficiency, but the preliminary work suggests that this place may be one of importance. The procedure is too involved for use as a routine, except in institutions in which full laboratory facilities are available, and it is not justified even here unless it gives information that is not available from any other source. In the seven cases considered there is something definitely abnormal in the rate of excretion of sulphate when the other tests show the kidney to be functioning normally. That the fault in some of these cases, particularly those in which there were nephrotic tendencies, may be outside the kidney is a possibility, but the presence of renal injury as a contributing factor is difficult to exclude. There can be no doubt that the clearance of sulphate is lowered in the presence of definite renal injury, and this is true whether or not edema is present.

The value for sulphate clearance which has been chosen as the lower limit of normal is probably too low, in that it is considerably below the average obtained in work with normal subjects. The figures which have been chosen as a minimum normal for urea clearance represent approximately 80 per cent of the average found among normal subjects by Moller, McIntosh and Van Slyke,¹³ whereas 20 for the sulphate clearance represents only 59 per cent of the normal average as determined from table 2 of this report. A clearance of 25 or less should warrant further investigation, and if on repeated tests no higher value is obtained, the presence of impaired function must be seriously considered. In this series, however, in which there was only one reading in many of the cases, the low minimal value has been used to avoid inclusion of questionable results.

Emphasis should be given again to the factors which must be controlled when one is working in this field, particularly the intake of food. The actual conditions in this respect are not so important as long as

18 Shannon, J. A., Jolliffe, Norman, and Smith, H. W. The Excretion of Urine in the Dog. VI. The Filtration and Secretion of Exogenous Creatinines, *Am. J. Physiol.* **102**: 534 (Dec.) 1932.

they are always the same, and as long as the same conditions are maintained in establishing the normal. The bladder must be carefully emptied after the proper interval, and all of the urine must be saved. In working with small volumes of urine, a loss of 2 or 3 cc will introduce a large percentage of error. The actual laboratory technic must be as accurate as in any complicated procedure, unless this is done, there is always the chance for error to appear in an occasional determination.

SUMMARY AND CONCLUSIONS

1 When a person is following a regimen of fasting, the excretion of inorganic sulphate is fairly constant throughout the day, whereas when he is receiving a normal diet there is considerable variation. The value for serum sulphate under similar circumstances changes much less.

2 Inorganic sulphate is concentrated less in the urine than is either urea or creatinine, and the clearance of sulphate tends to maintain a more constant level than that of either of the other two substances.

3 The sulphate clearance is relatively independent of wide changes in the volume of the urine.

4 With definite renal insufficiency the sulphate clearance is reduced in a great majority of instances, although in some cases it is normal when other tests indicate impaired function.

5 The sulphate clearance of six patients was normal in the presence of an elevated value for serum sulphate. At present the explanation of this is not clear.

6 In 12 per cent of a series of fifty-eight cases of definite or suspected renal disease, the sulphate clearance indicated impaired renal function when all of the other tests gave figures within normal limits.

THE CHOLESTEROL AND VITAMIN A CONTENT OF THE LIVER IN MAN

A STUDY OF ONE HUNDRED AND SIX LIVERS OBTAINED AT AUTOPSY

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AND

M M SUZMAN, M D ¹

BOSTON

Few data on the cholesterol content of the liver in man are available. In 1913, Grigaut ¹ found an average of 0.35 Gm per hundred grams of human liver. In the following year, Landau and McNee ² recorded the cholesterol content of the liver in nine cases as varying from 0.18 to 0.46 Gm per hundred grams of fresh liver. Since that time a few scattered observations have been reported. The most extensive study was made by Fex, ³ who determined the content of cholesterol in the liver in twenty-two cases. He found that the normal range was between 0.254 and 0.396 Gm per hundred grams, while in the pathologic liver the cholesterol varied from 0.241 to 0.43 Gm per hundred grams.

The cholesterol content of the liver in one hundred and six cases in which postmortem examinations were made is reported in this paper. Incidentally, the same autopsy material was used by one of us (Suzman) for vitamin A determinations. As no studies are available correlating the vitamin A and the cholesterol content of the liver, it was thought of interest to correlate them, especially since Takahashi and Nakamiya ⁴ had reported that vitamin A belongs to the group of substances classified as sterols. Seel ⁵ recently reported that a purified substance containing

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, the Department of Medicine, Harvard Medical School, and the Massachusetts General Hospital.

1 Grigaut, A. *Le cycle de la cholestérinémie*, Paris, G. Steinheil, 1913.

2 Landau, M., and McNee, J. W. *Zur Physiologie des Cholesterinstoffwechsels*, *Beitr z path Anat u z allg Path* **58** 667, 1914.

3 Fex, J. *Chemische und morphologische Studien über den Cholesterin und die Cholesterin Ester in normalen und pathologisch veränderten Organen*, *Biochem Ztschr* **104** 82, 1920.

4 Takahashi, K., and Nakamiya, J. *Physiological Significance of Biosterin (So-Called Vitamin A)*, *Jap M World* **5** 2, 1925.

5 Seel, H. *Ueber die chemische Natur des antizeroththalmischen Vitamins "A,"* *Arch f exper Path u Pharmacol* **159** 93, 1931.

vitamin A gave cholesterol reactions which paralleled the biologic test for vitamin A, and that this substance was soluble in the usual solvents for sterols. He feels, therefore, that although positive proofs are lacking, his investigations corroborate those of Takahashi and Nakamya, and that his findings make it probable that vitamin A is an intermediary product of the cholesterol metabolism. In a comprehensive review of work on the vitamins, Browning⁶ also decided that the results of prolonged investigations into the nature of vitamin A prove that it belongs to the sterol class of substances, allied to cholesterol or ergosterol. Further, it has been shown experimentally⁷ that mice suffering from avitaminosis A have less cholesterol in the liver than do normal mice.

MATERIAL AND METHODS

The material was obtained in a series of one hundred and six autopsies at the Massachusetts General Hospital, Boston City Hospital and Beth Israel Hospital. At the autopsy varying amounts of hepatic tissue were placed in air-tight jars of known weight, each containing 50 cc of 40 per cent aqueous potassium hydroxide. These were then reweighed to ascertain the exact amount of liver in each. On standing, saponification of the liver took place, this process was completed by heating the jars in a bath of boiling water for fifteen minutes. The content of each jar was then measured and diluted with distilled water to a definite volume. The material was stored until it was convenient to carry out the estimations. It was ascertained that storage did not affect appreciably the amount of cholesterol in the liver.

The method used for carrying out the determinations of cholesterol in the liver has been described by Cornell⁸. It proved reliable in our hands. Cornell's experience that ether as the extracting fluid gave little or no interfering coloration was verified. All of the determinations were carried out in duplicate and, occasionally, triplicate.

The amount of vitamin A in these livers was determined by one of us (Suzman)⁹.

6 Browning, E. The Vitamins, Monogr. Pickett-Thomson Research Lab., 1931, no. 1.

7 Javillier, M., Rousseau, S., and Emerique, L. La composition chimique des tissus dans l'avitaminose A. Phosphore, extrait lipidique, cholesterol, *Compt rend Acad d sc* **188** 580, 1929.

8 Cornell, B. S. Accurate Colorimetric Technique for Blood and Tissue Cholesterol Estimations, *J Lab & Clin Med* **14** 251, 1928.

9 For this purpose portions of liver removed at autopsy were placed in 50 cc of a 40 per cent aqueous solution of potassium hydroxide. After saponification, the material was extracted three times with petroleum ether. After being washed with water several times until there was no tendency to form an emulsion, and after dehydration by means of anhydrous sodium sulphate, the layer of petroleum ether was evaporated to dryness under partial pressure in an atmosphere of carbon dioxide. The residue, consisting of the unsaponifiable fraction, was dissolved in a known amount of chloroform and assayed for its vitamin A content by the antimony trichloride method of Carr and Price (*Biochem J* **20** 497, 1926), the Rosenheim-Schuster modification of the Lovibund tintometer being used. The results are expressed in blue units per gram of tissue "per centimeter cube," according to the method of Moore (*Biochem J* **23** 1267, 1929).

RESULTS

The amount of cholesterol in the livers in the one hundred and six cases studied varied from 0.098 to 1.003 Gm per hundred grams, with an average of 0.301 Gm. The actual distribution of the cholesterol values is illustrated in the chart.

The relation of vitamin A to cholesterol is illustrated in table 1. Discarding the two extreme cases, the coefficient of correlation is 0.036 ± 0.067 , a value showing no correlation. The cholesterol curve is slightly skewed to the left, while the sample of cases with respect to the vitamin A content shows extreme skewness (chart). Forty-seven of the one hundred and six cases, or 44.3 per cent, showed vitamin A

TABLE 1—*The Quantitative Relation of Cholesterol to Vitamin A in the Liver in One Hundred and Six Cases*

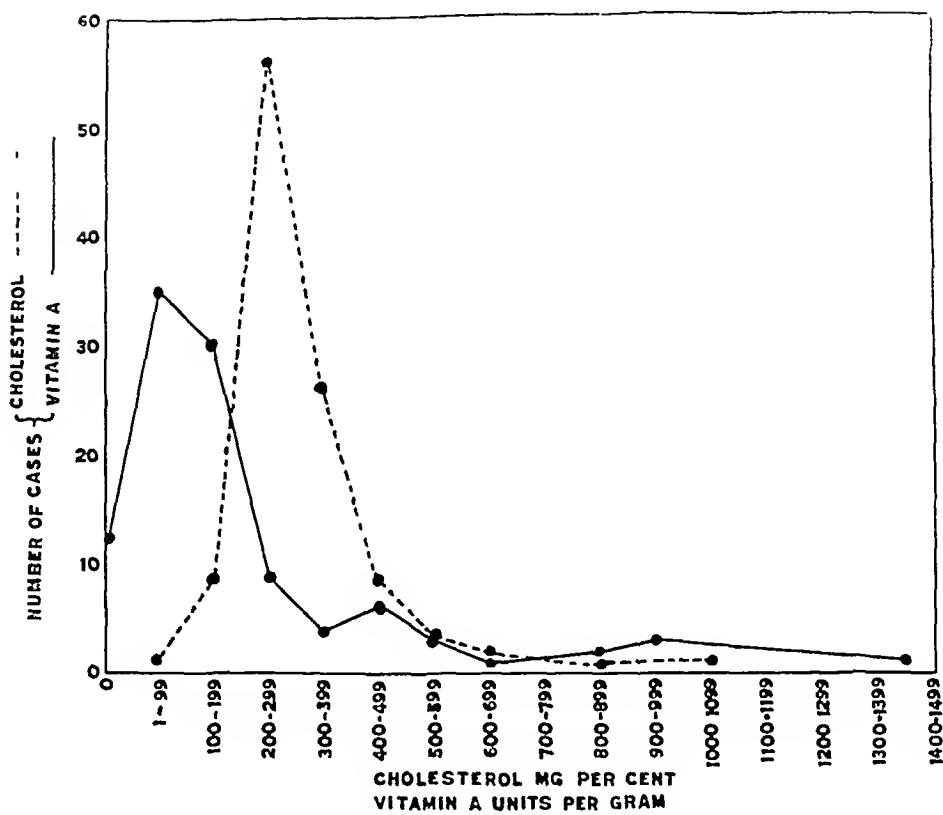
Cases	Per Cent of Total Number	Vitamin A, Units per Gram	Cholesterol, Mg per 100 Gm							
			0-99	100-199	200-299	300-399	400-499	500-599	600-699	700-799
47*	44.34	0-99	1	6	25	9	2	1	1	1
30	28.30	100-199			14	11	3	2		
9	8.49	200-299		1	5	2	1			
4	3.77	300-399		1	2		1			
6	5.66	400-499			3	2			1	
3	2.83	500-599			2		1			
1	0.94	600-699			1					
		700-799								
2	1.90	800-899			2					
3	2.84	900-999			1	2				
		1000-1099								
		1100-1199								
		1200-1299								
		1300-1399								
1	0.94	1400-1499			1					
Cases			1	8	56	26	8	3	2	1
Per cent of total number			0.94	7.55	52.83	24.52	7.55	2.84	1.84	0.94

* The cholesterol of the liver in one case not recorded in the table was 1,003 mg per hundred grams.

values below 100 blue units per gram of liver tissue, and of these twelve, or 11.3 per cent, showed complete absence of vitamin A, while eighty-four, or 79.2 per cent, had a cholesterol content of from 200 to 400 mg per hundred grams. Cholesterol was never absent in any liver, which indicates that this substance is an integral part of the liver tissue.

Statistically no significant differences in the cholesterol content of the liver between the two sexes could be made out. The average and its standard deviation for the sixty males were 290 ± 13.3 mg per hundred grams, and for the fifty-six females, 325 ± 19.2 per hundred grams. The difference and its standard deviation were 35 ± 23.4 —values which cannot be considered significant.

The age of the one hundred and six patients at death ranged from 10 months to 81 years. The coefficient of correlation of the age and



The distribution of cholesterol and vitamin A in the liver in one hundred and six cases. Cholesterol is represented by the broken line and vitamin A by the unbroken line. Milligrams per hundred grams of tissue (cholesterol) and units per gram (vitamin) are shown below. The grouping of cases is shown at the left.

TABLE 2—The Amount of Cholesterol in the Liver in Various Diseases

Diagnosis	Cases	Cholesterol, Mg per 100 Gm								
		0-99	100-199	200-299	300-399	400-499	500-599	600-699	700-799	
Acute infection	33	1	4	24	4					
Tuberculosis	11		2	8	1					
Operative death	5		1	4						
Thrombosis	6			2	4					
Acute anterior poliomyelitis	2			2						
Syphilis	1			1						
Internal hemorrhage	1			1						
Chronic nephritis	2			1	1					
Diabetes mellitus	1			1						
Pulmonary embolism	1			1						
Acute and subacute endocarditis	6			2	2		1	1		
Sarcoma	2			2						
Malignant lymphoma	1			1						
Carcinoma	15			5	5	4			1	
Hypertension*	9			2	4	1		1		
Plasmacytoma	1				1					
Myelogenous leukemia	1				1					
Perleukemic anemia	1				1					
Lipoid nephrosis	1					1				
Thyroid toxicosis	1					1				
Pemphigus	1						1			
Alcoholic cirrhosis	1						1			

* The cholesterol of the liver in one case not recorded in the table was 1,000 mg per hundred grams.

the cholesterol content of the liver was 0.140 ± 0.066 , indicating that no significant relation existed between these two factors

It is evident that in autopsy material from general hospitals the disease processes are not, as a rule, clearcut and that several conditions may be present in the same person. An attempt, however, has been made to classify the one hundred and six cases according to the diseases considered to be the chief causes of death. The relation of the cholesterol in the liver to the disease process is shown in table 2. Unfortunately, there are too few cases in each division to be significant. If one groups them in three main groups (table 3), it is clear that infections are associated with a lower cholesterol content than are malignant tumors or arterial hypertension, and that malignant tumors are associated with somewhat lower cholesterol values than is hypertensive disease. The hypertensive group is small, but the results are suggestive.

TABLE 3—*Cholesterol in the Liver Related to Three Groups of Disease Processes**

Diagnosis	Number of Cases	Cholesterol, Mg per 100 Gm									
		0-99	100-199	200-299	300-399	400-499	500-599	600-699	700-799	1000-1099	
Acute and chronic infection	53	1 (1.9)	6 (11.3)	37 (70.0)	7 (13.2)		1 (1.9)	1 (1.9)			
Malignant tumors	20			8 (40.0)	7 (35.0)	4 (20.0)			1 (5.0)		
Hypertension	9			2 (22.2)	4 (44.4)	1 (11.1)		1 (11.1)		1 (11.1)	

* The number in parenthesis indicates the percentage of the number in each group

COMMENT

It is evident that the cholesterol content of the liver, even in pathologic material, is remarkably constant in comparison with the content of vitamin A, indicating that the cholesterol in the liver is probably an integral part of the hepatic protoplasm. It may be assumed, perhaps, that in the normal liver the cholesterol content varies within an even narrower range, while there is suggestive evidence that in healthy man the vitamin A in the liver may be absent or low. In seventy-eight cases of accidental death Wolff¹⁰ found a range between 0 and 1,210 blue units, and in nine of these cases, less than 50 blue units. This variation of vitamin A in the liver of normal man corresponds to the values found by Wolff and by us in the livers of patients dying from various disease processes.

In addition to the fact that there seemed to be a tendency toward relatively low cholesterol values in the livers of patients who died from

¹⁰ Wolff, L. K. On the Quantity of Vitamin A Present in the Human Liver, *Lancet* 2: 617, 1932

chronic and acute infection and toward high values in patients with hypertensive disease as the primary cause of death, a few observations of interest are herewith recorded. In two conditions, namely, diabetes mellitus and pernicious anemia, it has been definitely established that there exists a disturbed cholesterol metabolism. In seven cases of diabetes mellitus collected from the literature,¹¹ the cholesterol content of the liver varied from 0.241 to 0.32 Gm per hundred grams, figures corresponding to the average values reported as normal and agreeing with the amount of cholesterol found in the liver in one case of diabetes in this series. In two cases of pernicious anemia reported by Fex,³ the cholesterol content of the liver was 0.397 and 0.423 Gm per hundred grams, corroborating the value found by us in one patient inadequately treated for five days with liver extract. The values found in pernicious anemia are somewhat higher than the general average. It is evident, therefore, that Hueck's¹² contention as to hypercholesteremia and deposits of cholesterol in the tissues, so far as the liver is concerned is not verified with regard to diabetes mellitus. In this connection it may be pointed out that Nitzescu and his co-workers¹³ demonstrated in dogs that a normal deposit of cholesterol in the liver and lungs was prevented if the pancreas was removed. On the other hand, in pernicious anemia there seems to be a tendency toward overstorage of cholesterol in the liver and pathologic infiltration of the organ by it, although the cholesterol content of the blood during the relapse is greatly decreased. This has been interpreted by Piney¹⁴ as being due to an overstimulation of the normal mechanism for the storage of fat. Landau and McNee² pointed out that the liver does not seem to store cholesterol in hypercholesteremia but does store it in hypocholesteremia. Whether this is universally true can be determined only by further investigation of the cholesterol content of tissues in specific diseases, data are not now available in sufficient amount to draw definite conclusions.

SUMMARY

The cholesterol content of the liver at autopsy in one hundred and six cases ranged from 0.098 to 1.003 Gm per hundred grams, with an

11 Rewald, B. Der Cholesteringehalt normaler und pathologischer menschlicher Organe, *Biochem Ztschr* **99** 253, 1919. Klemperer, G., and Ueber, H. Zur Kenntnis der diabetischen Lipämie, *Ztschr f klin Med* **65** 340, 1908. Fex,³

12 Hueck, W. Referat über den Cholesterin Stoffwechsel, *Verhandl d deutsch path Gesellsch* **20** 18, 1925.

13 Nitzescu, I. I., Propescu-Inotesti, C., and Cadariu, I. L'insuline et la cholesterinémie, la cholesterinémie dans le diabète expérimental, *Compt rend Soc de biol* **90** 538, 1924. Nitzescu, I. I., and Cadariu, I. L'insuline et le métabolisme de la cholestérine, *ibid* **92** 296 1925.

14 Piney, A. Recent Advances in Haematology, Philadelphia, P. Blakiston's Son & Co. 1927.

average of 0.301 Gm. Statistically no relation could be established between the cholesterol and the vitamin A content of the liver or the sex or the age of the patient.

The cholesterol content of the liver tended to be lower than the average in patients who died of infections, and highest in those who died of arterial hypertensive disease, with those who had malignant tumors as a cause of death occupying an intermediary position.

Dr. J. Lerman, Massachusetts General Hospital, permitted me to use his statistical analysis of the data.

ESSENTIAL FRUCTOSURIA

REPORT OF THREE CASES WITH METABOLIC STUDIES

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AND

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Fructosuria, otherwise termed "levulosuria," was recognized soon after polarization of urines for the detection of sugar became common. In 1840, Biot¹ first examined urine in the polariscope, but it remained for von Gorup-Besanez² to describe in urine a "levorotatory noncrystallizable sugar that behaves like fructose." The early observers had no rapid accurate chemical test for the identification of fructose before Selivanoff³ introduced the use of concentrated acid and resorcinol for the identification of this sugar. Although the specificity of his test has been questioned many times, it is still an excellent method for detecting even very small quantities of fructose, alone or in the presence of other sugars, especially if the precautions outlined by Borchardt⁴ are followed.

We are able to add three new cases of fructosuria to the twenty-seven described in the literature since 1876, when the anomaly was first recognized.⁵ The only case of essential fructosuria described in the

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1 Biot, M. *Compt rend Soc de biol* **11** 1028, 1840

2 von Gorup-Besanez. *Anleitung zur Zoochemischen Analyse*, quoted by Seegen. *Centralbl f d med Wissensch* **22** 753, 1881

3 Selivanoff, T. *Ber d deutsch chem Gesellsch* **20** 181, 1887

4 Borchardt, L. *Ztschr f physiol Chem* **55** 241, 1908

5 (a) Zimmer, K. *Deutsche med Wchnschr* **2** 329 1876. Czapek. *Prag med Wchnschr* **1** 265, 1876. (b) Seegen, J. *Centralbl f d med Wissensch* **22** 753, 1884. Kulz, E. *Ztschr f Biol* **27** 228 1890. (c) May, R. *Deutsches Arch f klin Med* **57** 279, 1896. (d) Spath and Weil. *Med-Cor-Bld wurttemb arztl Landesver* **72** 717, 1902, quoted by Rosin. *Beitr z wissenschaft f Med u Chem (Festschr E Salkowski)*, 1904, p 105. (e) Rosin, H., and Leband, H. *Ztschr f klin Med* **47** 182, 1902. (f) Brodersen. *Inaug Dissert*, Kiel, 1903. (g) Schwarz, L. *Deutsches Arch f klin Med* **76** 231, 1903. (h) Lion, A. *Munchen med Wchnschr* **50** 1105 1903. (i) Schlesinger, W. *Arch f exper Path u Pharmacol* **50** 272, 1903. (j) Lepine, R., and Boulud. *Rev de med*, Paris **24** 185, 1904. (k) Neubauer, E. *Munchen med Wchnschr* **52** 1525, 1905. Note by Jolles, A. *Wien med Presse* **47** 2301, 1905. (l) von Morawski, *Ztschr f klin Med* **64** 503, 1907. (m) Koenigsfeld, H. *ibid* **69** 291,

Footnote continued on next page

American literature is that which Strouse and Friedman⁶ reported in 1912

IDENTIFICATION AND QUANTITATIVE DETERMINATION OF FRUCTOSE IN THE URINE

Like other keto-sugars, fructose reduces Fehling's solution even at room temperature, as was emphasized recently by Lasker and Enklewitz⁷ Fructose, like dextrose, is easily fermented by common yeast, which differentiates it from ketopentose, the reducing substance passed by patients with essential pentosuria

The Selivanoff reaction is specific for the keto-sugars and can detect them even in the presence of large amounts of dextrose. The urine is brought to a boil with an equal volume of 25 per cent hydrochloric acid. A few crystals of resorcinol are added, and the urine is boiled for only ten seconds. A heavy red precipitate, soluble in alcohol, indicates the presence of fructose

Fructose can be further differentiated from dextrose by the readiness with which it forms an osazone in an acid solution with methylphenylhydrazine⁸

If fructose is the only sugar present in the urine, the values obtained by polarization, reduction and fermentation should coincide. If, however, both fructose and dextrose are present, the relative amounts may be computed by a comparison of the rotation and reduction values

Fructose has a specific rotation of $-93.6^{\circ} + 0.64^{\circ} \times (t^{\circ} - 20)$ Laborde⁹

In all of our studies, the urinary sugars were quantitatively determined by the method of Beitland¹⁰ or Benedict¹¹ Quantitative fer-

1909 (three cases) (n) Adler, O. *Arch f d ges Physiol* **139** 93, 1911 (two cases) (o) Strouse, S., and Friedman, J. C. *Arch Int Med* **9** 99, 1912 (p) Barrenscheen, H. K. *Biochem Ztschr* **127** 222, 1922 (q) Steinberg, S., and Elberg, W. *Klin Wchnschr* **4** 2399, 1925 (three cases) (r) Snapper, J., van Creveld, S., and Grunbaum, A. *Arch f Verdauungskr* **38** 1, 1926 (s) Heeres, P. A., and Vos, H. *Fructosuria*, *Arch Int Med* **44** 47 (July) 1929 (t) Ansel, N. *Klin Wchnschr* **9** 1400, 1930 (u) Fischer. *Jahrb f Kinderh* **131** 341, 1931 (v) Steinitz, F. *Deutsches Arch f klin Med* **171** 401, 1931

6 Strouse, S., and Friedman, J. C. *Levulosuria, with a Report of an Unusual Case*, *Arch Int Med* **9** 99 (Jan) 1912

7 Lasker, M., and Enklewitz, M. *J Biol Chem* **101** 289, 1933

8 Neuberg, C. *Ztschr f physiol Chem* **36** 227, 1902

9 Laborde. *Ann fals* **6** 650, 1913

10 Bertrand G., and Thomas, P. *Practical Biological Chemistry*, London, Bell and Sons, 1920

11 Benedict, S. R. *The Detection and Estimation of Glucose in the Urine*, *J A M A* **57** 1193 (Oct 7) 1911

mentations were carried out in the van Iterson-Kluyver apparatus¹² at room temperature for twenty-four hours. Blood sugars were determined in venous blood by the method of Folin and occasionally in capillary blood by the Hagedorn-Jensen procedure. Blood fructose was estimated by the method of van Creveld.¹³

The identification of fructose should never be undertaken on an alkaline urine, because there is a possible conversion of dextrose into fructose in alkaline solutions.¹⁴

Levorotation may be due to substances other than fructose, for example, hydroxybutyric acid, conjugated glycuronic acids and some amino-acids.

To establish primary fructosuria unequivocally, the following criteria must be met by an acid urine:

- 1 Reducing sugar must be present and active at room temperature.
- 2 The urine must ferment with ordinary yeast.
- 3 The urine must be levorotatory, and the levorotation must disappear after fermentation.
- 4 The Selivanoff reaction, with the proper precautions, must be positive.
- 5 The methyl-phenyl osazone should be isolated and its chemical and physical constants determined. The quantitative values for 1, 2 and 3 should agree.

REPORT OF CASES

CASE 1—The patient was an American boy, aged 22 years, of Italian parentage. His previous history was essentially negative, except that he had never been particularly robust. There was one maternal uncle who was said to have had diabetes mellitus. One year before the patient's entrance into the Mount Sinai Hospital he had been rejected for life insurance on the ground that he had glycosuria. At no time was there polyuria, polydipsia, polyphagia, loss of weight or any other symptoms associated with diabetes mellitus in young people. He entered the hospital because of severe pain in the lower part of the abdomen of several days' duration without fever or vomiting. A complete laboratory and physical examination failed to reveal any organic cause for the abdominal complaint. The results of physical examination were essentially negative, except that the patient was slightly undernourished and of rather nervous temperament. The blood pressure was 114 systolic and 66 diastolic.

Laboratory Examination—The hemoglobin was 95 per cent, the red blood cell count was 4,600,000, and the white cell count, 8,800, the polymorphonuclears were 57 per cent, the lymphocytes 40 per cent, and the monocytes 3 per cent. The smear was normal. The Wassermann test of the blood was negative. The blood showed 265 mg of cholesterol per hundred cubic centimeters, of which 100 mg was esterified. The blood also showed 85, 100 and 90 mg of sugar per hundred cubic centimeters. The urine was normal and contained only normal quantities

¹² van Iterson, G., and Kluyver, A. J., quoted by van der Haar, A. W. *Anleitung zum Nachweis der Monosaccharide*, Berlin, Borntraeger, 1920.

¹³ van Creveld, S. *Klin. Wchnschr.* **6**: 697, 1927.

¹⁴ Lobry de Bruyn, C. A. *Rec. d. trav. Chim., Pays-Bas* **14**: 156, 1895; also *Ber. d. deutsch. chem. Gesellsch.* **28**: 3078, 1895.

of urobilin Roentgen examination of the gastro-intestinal tract and the urinary tract revealed no abnormalities

CASE 2—During the investigation of the family of the patient in case 1 it was discovered that the 12 year old brother had fructose in the urine. So far as we could learn, he showed no clinical evidence of disease. The criteria for the diagnosis of fructosuria were met in every respect

CASE 3—A girl, aged 17 years, entered the hospital for the relief of severe, recurrent angioneurotic edema. Her father and paternal uncle were said to have

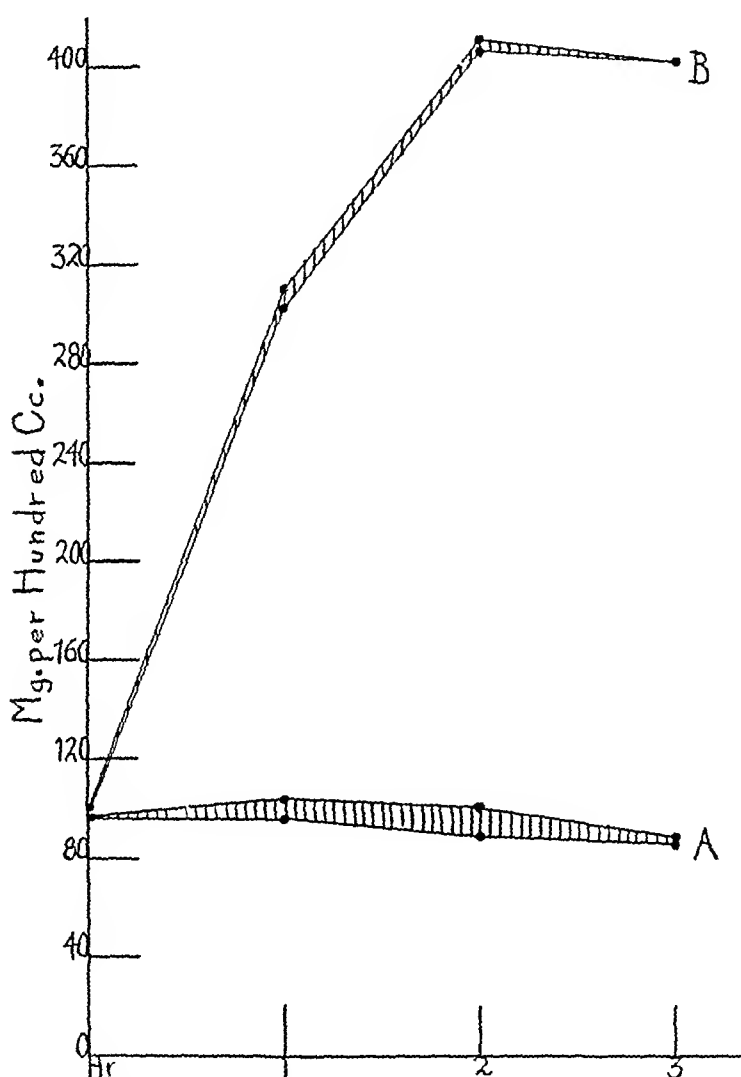


Chart 1—The curves of total reducing substance, fructose and dextrose in the blood after oral administration of 50 Gm of fructose. *A*, in a normal patient, and *B*, in a diabetic patient. In all of the charts, the upper curve represents the total reducing substance, the lower curve, dextrose, and the shaded portion, the amount of fructose present

"sugar in the urine but no diabetes." In her own previous history there was little of significance. Two years prior to admission she was advised of the presence of sugar in the urine. Careful diet and the use of insulin have been of no avail in attempts to control the glycosuria. For six months she had had severe attacks of sudden swellings of various parts of the body, with itching and malaise. Attempts to find an allergic basis for the symptoms failed.

Physical examination revealed a well nourished, normally developed girl of 17 years. Except for areas of angioneurotic edema involving the fingers, nothing of significance was noted. During her stay in the hospital there was involvement of the skin of the face, eyelids, feet, tongue and labia majora by the edema.

Treatment by restriction of the diet and administration of ergotamine, calcium, ephedrine and thyroid extract was absolutely without effect on the frequency or the severity of the attacks. Epinephrine gave some relief.

The laboratory findings were hemoglobin, 70 per cent, leukocyte count, 12,000, polymorphonuclears, 52 per cent, lymphocytes, 43 per cent, eosinophils, 1 per cent, monocytes, 2 per cent, and myelocytes, 1 per cent. Except for the presence of fructose, the urine was normal. The Wassermann reaction of the blood was negative. The blood sugar during fasting averaged 75 mg per hundred cubic centimeters. The van den Bergh reaction and the icteric index were normal. No dye was retained after bromsulphalein was administered intravenously. The dextrose tolerance curve was normal.

The basal metabolic rate was minus 20 per cent. The patient was given thyroid extract by mouth, and after several weeks the basal metabolic rate rose to plus 18 per cent. After fructose was administered by mouth, the urinary fructose rose to 5 per cent. Further studies in this case are reported later in this paper.

We were able to examine the urine of the patient's father and could establish unequivocally that the reducing substance present was not fructose but pentose. We wish to note the possible significance of this familial incidence of ketosuria.

EXPERIMENTAL RESULTS

The observations were made in case 1 unless otherwise indicated.

Identification of the Reducing Substance—The early morning specimens taken at least twelve hours after the previous meal were often fructose-free. At other times, on the usual diet of the ward, the sugar varied between 0.2 and 1.5 per cent. That the entire reducing substance was fructose can be seen from these comparative studies of a typical specimen of urine.

	Per Cent
Fructose by reduction (Bertrand)	3.65
Fructose by fermentation	3.40
Fructose by polarization	3.55

If any dextrose or pentose had been present the levorotation would have been lower, and the presence of pentose would also have resulted in lower fermentation than reduction values. The methyl-phenyl osazone was prepared from the patient's urine and compared with one from pure fructose. The crystals were identical, melting at 154 C., and the melting point was unaltered by mixing.

Effect of the Withdrawal of Fructose—The variations in the concentrations of fructose when the patient was given the diet of the ward indicated that the source of the urinary sugar was alimentary. When the patient was placed on a diet completely free from fructose, the fructosuria disappeared and was absent as long as this diet was maintained.

Dextrose Tolerance—The patient reacted normally on ingestion of dextrose, of which he was given 0.66 Gm per kilogram of body weight in 500 cc of water after a fourteen hour fast. The urine remained sugar-free.

Galactose Tolerance—Forty grams of galactose was administered in 500 cc of water fourteen hours after the last meal. No reducing substances were found in the urine.

TABLE 1—*Total Sugar in the Blood of a Fructosuric Patient Following Ingestion of Dextrose*

Time	Mg per 100 Cc of Blood	
	February 6, 1933	February 10, 1933
During fasting	85	80
1 hour after ingestion of dextrose	100	115
2 hours after ingestion of dextrose	85	95
3 hours after ingestion of dextrose	80	86
4 hours after ingestion of dextrose	75	74

TABLE 2—*Urinary Excretion of Ingested Fructose*

Fructose Ingested, Gm	Percentage of Fructose Excreted in 24 Hours (Average of at Least Two Experiments)
1	Traces
5	16
25	11
50	12
75	14
100	14

TABLE 3—*Urinary Excretion of Intravenously Injected Fructose*

	Fructose Injected, Gm	Fructose Excreted, Gm	Percentage Excreted	Duration of Fructosuria
Control	15	0.65	4.3	15 minutes
Fructosuric patient	15	2.01	13.4	2 hours

Quantitative Excretion of Fructose—During all of our studies, the patient was kept on a fructose-free diet and the urine was always sugar-free except when he was fed known amounts of fructose. The sugar was always given early in the morning after a fast of from twelve to fourteen hours. The greatest excretion took place in the first two hours and was practically complete in six hours. The administration of only 1 Gm of fructose caused the urine to give a faint reduction and a definite Selivanoff reaction. The urinary excretion of fructose when it was fed in amounts of from 5 to 100 Gm may be seen in table 2.

Fifteen grams of fructose in a 30 per cent solution was injected intravenously into a normal control and into the patient. The urinary excretion of fructose is given in table 3.

Effect of Other Carbohydrates on Excretion of Fructose—The simultaneous administration of another carbohydrate caused a definite increase in the amount of fructose excreted. The tests showed fructose but no other sugar in the urine.

Effect of Fructose on the Total Sugar and on the Fructose in the Blood of a Normal Control, a Diabetic Patient and a Patient with Essen-

TABLE 4—*Urinary Excretion of Fructose After Simultaneous Administration of Another Carbohydrate*

Carbohydrates Ingested	Percentage of Total Fructose Excreted
50 Gm fructose	12
50 Gm fructose + 50 Gm dextrose	21
50 Gm fructose + 40 Gm galactose	21
95 Gm sucrose	19

TABLE 5—*Effect of Ingestion of 50 Gm of Fructose in a Fructosuric Patient, a Diabetic Patient and a Normal Control*

Time After Ingestion of Fructose	Control			Diabetic Patient			Fructosuric Patient		
	Total Sugar	Fructose	Dextrose	Total Sugar	Fructose	Dextrose	Total Sugar	Fructose	Dextrose
	Mg per 100 Cc of Blood	Mg per 100 Cc of Blood	Mg per 100 Cc of Blood	Mg per 100 Cc of Blood	Mg per 100 Cc of Blood	Mg per 100 Cc of Blood	Mg per 100 Cc of Blood	Mg per 100 Cc of Blood	Mg per 100 Cc of Blood
During fasting	97	0	97	100	0	100	90	0	90
1 hour	104	8	96	310	8	302	110	45	65
2 hours	100	12	88	410	4	406	115	55	60
3 hours	88	2	86	400	0	400	95	20	75

TABLE 6—*Effect of Epinephrine on the Total Sugar in the Blood of a Fructosuric Patient*

Time After Administration of Epinephrine	Total Sugar, Mg per 100 Cc
0 minutes	82
5 minutes	82
15 minutes	85
30 minutes	110
1 hour	147
2 hours	147
3 hours	110

trial Fructosuria—Fifty grams of fructose in 500 cc of water was fed to a normal control, a patient with diabetes mellitus and a fructosuric patient (case 1) after a fourteen hour fast. Table 5 and chart 1 show the comparative values in the three instances. The normal patient passed no sugar, the diabetic patient passed only dextrose, and the fructosuric patient passed the usual fraction of the total fructose.^{14a}

Effect of Subcutaneous Administration of Epinephrine on the Total Sugar and on Fructose in the Blood and on Fructose Tolerance—The effect of epinephrine alone is shown in table 6.

^{14a} Dobriner, K. Die alimentare Fructosämie, Thesis, Munich, 1933.

The effect of epinephrine on the fructose tolerance when 50 Gm of fructose was fed in the usual manner and 1 mg of epinephrine was simultaneously given subcutaneously is shown in table 7. The total fructose excreted was 15.4 per cent.

Epinephrine alone produced no glycosuria. The excretion of fructose from 50 Gm of fructose was unaltered by the administration of 1 mg of epinephrine. The fructose level in the blood did not differ essentially from that when fructose was fed without epinephrine.

Effect of Subcutaneous Administration of Insulin on Fructose Tolerance—Thirty units of insulin was administered subcutaneously at the

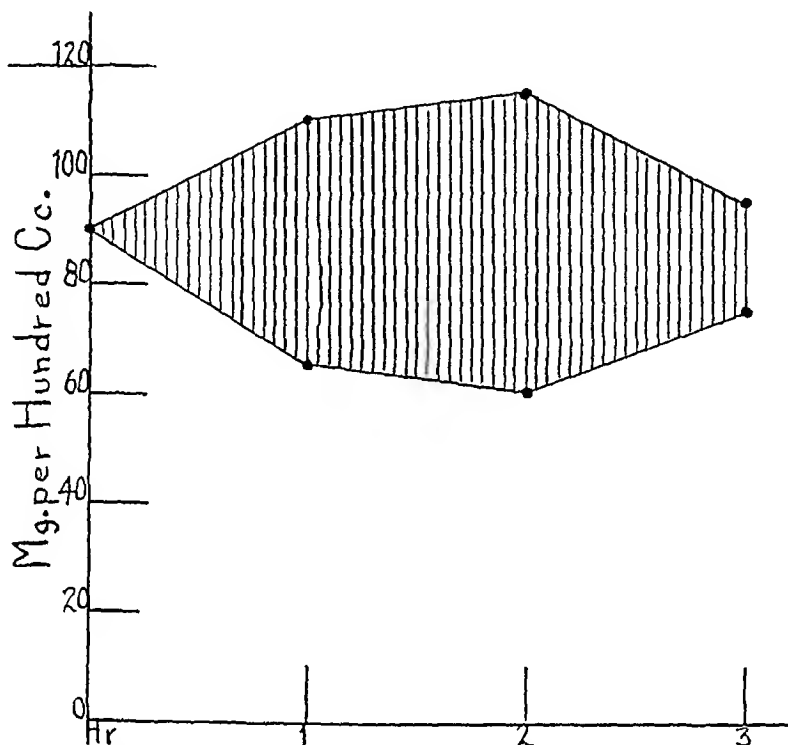


Chart 2—The curves of total reducing substance, fructose and dextrose in the blood after oral administration of 50 Gm of fructose in a fructosuric patient.

same time that 50 Gm of fructose was fed orally. The total fructose passed in the urine was diminished by the simultaneous administration of rather large amounts of insulin. The patient passed 14.6 per cent of the ingested dose with 20 units of insulin and 6.2 per cent with 30 units of insulin.

Effect of Oral Administration of Sorbitol in a Normal Control, a Diabetic Patient and a Fructosuric Patient—Fifty grams of *D*-sorbitol was dissolved in 500 cc of water and administered orally after a fourteen hour fast. The results are given in table 8. The urine of the normal control remained sugar-free. The urine of the diabetic patient contained 6.9 Gm of dextrose but no fructose, while the urine of the fructosuric patient contained 3.2 Gm of fructose and no dextrose.

Ingestion of Inulin—The patient was fed 50 Gm portions of inulin suspended in water and flavored with saccharin and vanillin. There was no rise in the blood sugar, and no fructose appeared in the blood or the urine. Intestinal fermentation was indicated by large amounts of gas in the intestine and slight diarrhea.

Results of Studies in Cases 2 and 3—The patient in case 2 was not available for hospital study, and we could obtain specimens of the urine only after the ingestion of fructose. The diagnosis of fructosuria was certain, since all of the criteria outlined earlier were met.

TABLE 7—*Effect of Epinephrine on Fructose Tolerance in a Fructosuric Patient*

Time After Administration of Epinephrine	Total Sugar, Mg per 100 Cc of Blood	Fructose, Mg per 100 Cc of Blood	Dextrose, Mg per 100 Cc of Blood
During fasting	100	0	100
1 hour	165	40	125
2 hours	135	54	81
3 hours	105	30	75

TABLE 8—*Effect of Administration of 50 Gm of d-Sorbitol in a Diabetic Patient, a Fructosuric Patient and a Normal Control*

Time After Administration of Drug	Control			Diabetic Patient			Fructosuric Patient		
	Total Sugar Mg per 100 Cc of Blood	Fructose Mg per 100 Cc of Blood	Dextrose Mg per 100 Cc of Blood	Total Sugar Mg per 100 Cc of Blood	Fructose Mg per 100 Cc of Blood	Dextrose Mg per 100 Cc of Blood	Total Sugar Mg per 100 Cc of Blood	Fructose Mg per 100 Cc of Blood	Dextrose Mg per 100 Cc of Blood
During fasting	110	0	110	180	0	180	80	0	80
1 hour	108	4	104	230	4	226	99	30	69
2 hours	97	4	93	260	0	260	104	35	69
3 hours	95	0	95	250	0	250	82	10	72

The patient in case 3 passed 10.1 per cent of fructose in the urine on one occasion, and on another 9.1 per cent after 50 Gm of fructose was given orally. After the basal metabolic rate had been raised by thyroid therapy, she excreted 8.4 per cent of the ingested 50 Gm, which is within the range of error of this type of experimentation. When 30 units of insulin was given with the 50 Gm of fructose, the excretion dropped to 5.8 Gm. She excreted 2.45 Gm of fructose after 50 Gm of sorbitol was given orally. The fructose excretion rose to 15.2 per cent when 50 Gm of dextrose was fed simultaneously with 50 Gm of fructose, and 16.8 per cent when 95 Gm of sucrose was fed.

COMMENT

Essential alimentary fructosuria is a specific, probably inborn, error of metabolism, characterized by the inability of the organism to utilize fructose normally and manifested clinically by a symptomless excretion

of fructose Fructose is passed in the urine only if fructose or substances capable of yielding it on digestion are ingested All of the reducing substances disappear from the urine if these foods are removed from the diet The usual sources of fructose are cane sugar, honey and fruit This disorder is not inconsistent with longevity (Steinitz' patient¹⁵ was 87 years old), and there is no reason to believe that it is a precursor of a diabetic state, although in some of the reported cases there was a family history of diabetes mellitus Transition from fructosuria to glycosuria has never been observed

The tolerance and metabolism of all of the other known carbohydrates are normal in this condition Dextrose, taken orally by the patient whom we studied, gave only the expected rise in blood sugar and caused no glycosuria, and the hyperglycemia reached the fasting level by the fourth hour Galactose was tolerated in a normal dose of 40 Gm

The addition of as little as 1 Gm of fructose to the patient's diet gave rise to fructosuria—a tolerance near the vanishing point, although we can scarcely speak of a tolerance in the true Hofmeister sense, i e, the amount expressed in grams of a carbohydrate that can be ingested without its appearance in the urine Tolerance, in its usual sense, implies that the tolerated amount is utilized, and that all beyond this is excreted The patient excreted a constant proportion of the ingested dose irrespective of the total amount taken (table 2) This phenomenon, for which no acceptable explanation is forthcoming, was first noted by Schlesinger¹⁵ in 1903 and has been found in all of the reported cases of essential fructosuria in which appropriate studies were made The route of the administration of fructose is apparently of no importance After oral and intravenous administration the same percentage of sugar is excreted

The simultaneous administration of another carbohydrate such as dextrose or galactose increases the excretion of fructose The burden placed on the carbohydrate-burning mechanism by the second sugar is perhaps enough to make the inability to utilize fructose more marked

Further insight into the nature of this rare anomaly is afforded by studies of the fructose and the dextrose in the blood The administration of 50 Gm of fructose by mouth (table 5) caused practically no rise in the blood sugar of a normal person, so rapidly was it fixed in the liver as glycogen When administered to the fructosuric patient, however, this dose caused a marked and sustained elevation of the blood sugar and fructosuria Even more striking differences were manifest when the blood sugar curves were resolved into their components, namely, fructose and dextrose It is assumed that the nondextrose-reducing substances remained constant, just as in the normal and pen-

15 Schlesinger, W Arch f exper Path u Pharmacol 50 272, 1903

tosuric children studied by Fischer and Reiner,¹⁶ as the nondextrose-reducing substances showed no change after the administration of dextrose

The normal person and the diabetic patient tolerated fructose so well that the level of this sugar in the blood rarely went above 10 mg per hundred cubic centimeters, a concentration below the renal threshold for fructose. The fructosuric patient could not handle the absorbed fructose normally. It accumulated in his blood, reaching a level of from 40 to 60 mg and passed into the urine.

It is apparent that in fructosuria there exists a deficiency in the mechanism that normally removes excessive fructose from the blood stream. This function was localized in the liver by Sachs,¹⁷ a pupil of Strauss, who in 1899 showed that hepatectomized frogs lost their ability to metabolize fructose. Later workers confirmed these findings for mammals in dogs with Eck fistula and in hepatectomized dogs.¹⁸ Essential fructosuria, therefore, has been looked on as representing a specific hepatic deficiency. It is clear from the clinical state of our patient and the results of the laboratory examinations that no hepatic disease exists in the usual sense of the term.

Another noteworthy point is the replacement of dextrose in the peripheral blood by another carbohydrate. It will be seen in chart 2 that the total blood sugar does not rise as high as would be expected if the level of the blood fructose were added to the original fasting level of the blood dextrose. Instead, the blood dextrose falls as the fructose rises, and thus tends to mask the full effect of the fructosemia. The replacement of dextrose in the blood by another carbohydrate has been noted previously. Sobotka and Reiner found that in the absorption of dextrose-galactose mixtures from the intestine of the rabbit the dextrose in the blood was replaced by galactose.¹⁹ Fischer and Reiner observed that in the administration of xylose to both pentosuric and normal children the pentose, although apparently nonutilizable, replaced the dextrose in some of the normal controls as well as in some of the pentosuric patients.¹⁶ This phenomenon is particularly clear in chart 4, in which it is shown how, under the action of insulin, dextrose practically disappeared from the blood of the fructosuric patient while fructose remained at 60 mg, seemingly high enough to prevent the symptoms of hypoglycemia.

16 Fischer, A. E., and Reiner, M. Pentosuria in Children, *Am J Dis Child* **40** 1193 (Dec.) 1930

17 Sachs, H. *Ztschr f klin Med* **38** 87, 1899

18 Mann, F. C. *Medicine* **6** 442, 1927. Jacobson, C. *Am J Physiol* **52** 233, 1920

19 Sobotka, H., and Reiner, M. *Proc Soc Exper Biol & Med* **27** 576, 1930

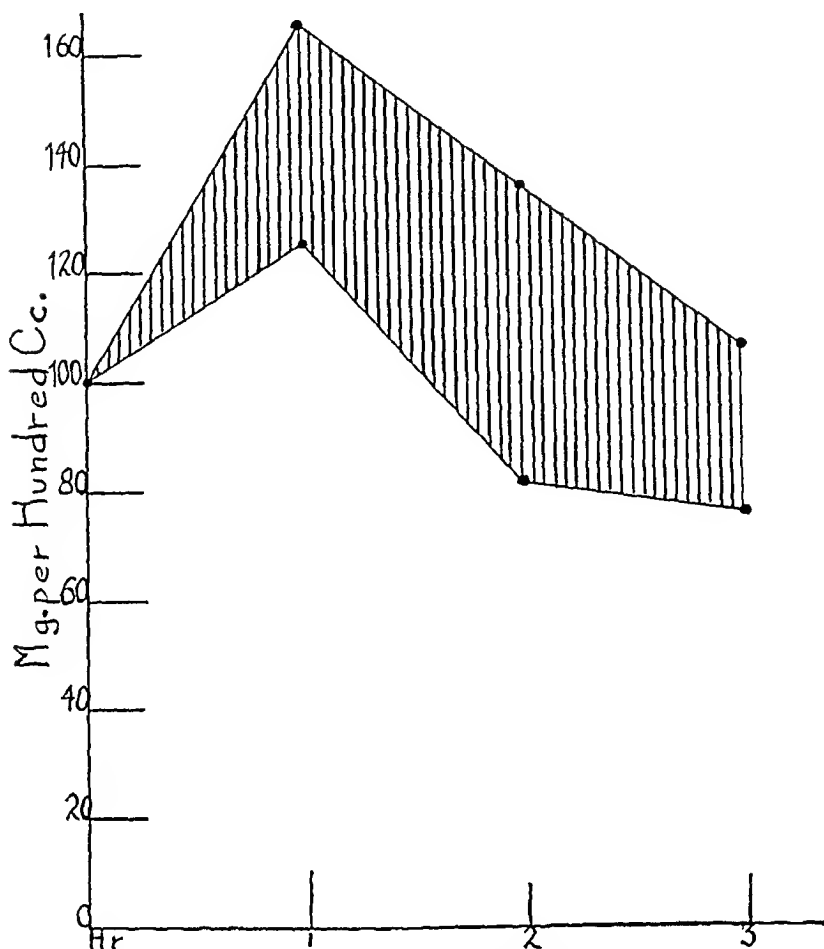


Chart 3—The curve of total reducing substance, fructose and dextrose in the blood after oral administration of 50 Gm of fructose and subcutaneous administration of 1 mg of epinephrine

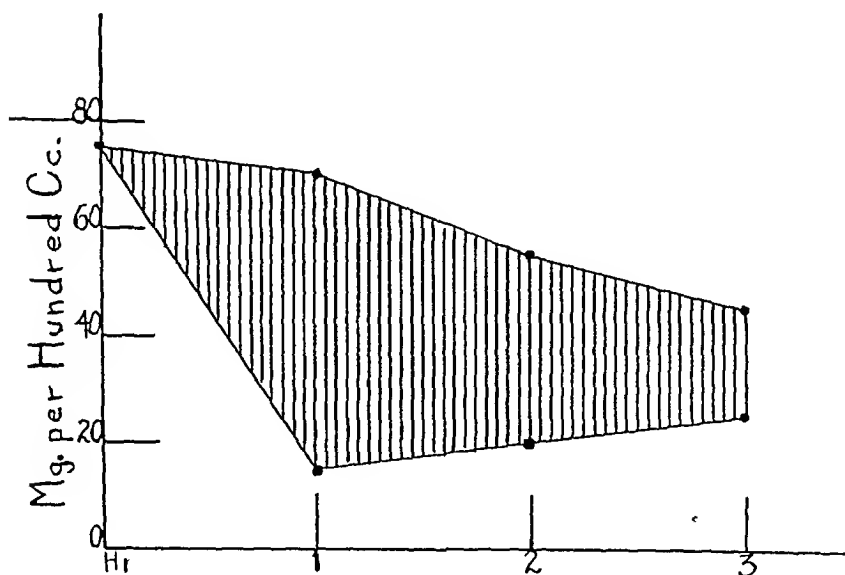


Chart 4—The curve of total reducing substance, fructose and dextrose in the blood after oral administration of 50 Gm of fructose and subcutaneous administration of 30 units of insulin

Epinephrine injected in a dose of 1 mg subcutaneously gave only the average hyperglycemic response and resulted in no glycosuria. When epinephrine and fructose were administered simultaneously, the blood sugar curve rose to a level indicating a summation—the hyperglycemia due to epinephrine and the rise due to the fructose. The fructose curve itself was unaltered, and only fructose was passed in the urine in the usual amount, 12 per cent of the amount ingested. Thus, epinephrine does not interfere with the usual utilization of fructose by the fructosuric patient, and the increased glycogenolysis caused by epinephrine does not alter the fructose tolerance.

The administration of fructose can prevent the appearance of hypoglycemic symptoms after insulin. It can be seen from chart 4 that this protection is not through the elevation of the blood dextrose via hepatic glycogen, but through a direct replacement of dextrose by fructose in the peripheral blood. With blood dextrose levels approaching zero, our patient showed only slight symptoms so long as fructose was circulating. The curve of the blood fructose after the administration of insulin did not differ much from that when insulin was not given. This is not surprising, as Minkowski²⁰ before 1880 knew that the processes by which fructose is fixed as hepatic glycogen proceed in the complete absence of the pancreas. Wierzuchowski²¹ showed with normal dogs that insulin does not affect the degree of fructosuria produced by the intravenous injection of fructose. The total excretion of fructose by our patient was slightly reduced when 30 units of insulin was given with 50 Gm of fructose.

In 1929, Thannhauser²² introduced *d*-sorbitol in the treatment of diabetes mellitus, claiming that this white, crystalline, pleasant-tasting solid could be utilized more efficiently than dextrose by diabetic patients. It has found considerable use abroad. Sorbitol does not reduce the usual sugar reagents. Its moderately laxative properties interfere somewhat with quantitative studies after oral administration. In our study, when sorbitol was given to a normal person, a slight rise in the blood sugar and no glycosuria resulted. When it was given to a diabetic patient it caused a hyperglycemia and the appearance in the urine of a sugar that could be identified as dextrose. In the fructosuric patient, a definite hyperglycemia resulted, and the blood fructose level reached 35 mg per 100 cubic centimeters, while the urine contained 3.2 Gm of fructose, 6.4 per cent of the ingested dose and no other sugar. Somewhere in the intermediary metabolism of sorbitol, fructose is formed. Normally, this is immediately fixed as hepatic glycogen, and there is no clue as to its

20 Minkowski, O. Arch f exper Path u Pharmacol **31** 167, 1893.

21 Wierzuchowski, M. J Biol Chem **68** 631, 1926.

22 Thannhauser, S. J., and Meyer. Munchen med Wchnschr **76** 356, 1929.

ever having been present. In our subject we had a person who could not metabolize fructose whether it was ingested preformed or was formed within his own organism. He had, so to speak, a biologic trap-door which allowed the fructose to pass into his urine and so manifest its presence.

It is perhaps significant that only one-half as much fructose was excreted by the patient from a dose of sorbitol as from a similar dose of fructose. It is possible that in the oxidation of the alcohol to the sugar one molecule yields dextrose and one fructose, the urinary fructose then represents the usual 12 per cent of the total fructose. This utilization of sorbitol via fructose may explain the fact that it is somewhat better tolerated than similar amounts of dextrose, as we know since Bouchardat and Kulz²³ that most diabetic patients utilize fructose better than dextrose.

Inulin and Jerusalem Artichokes (Helianthus Tuberosus)—Opinions in the literature diverge widely concerning the availability of inulin and Jerusalem artichokes (*Helianthus tuberosus*) to man. From our studies we favor the view that inulin is not digested or absorbed by man, and that any destruction of this polyfructoside that occurs results from bacterial action in the large bowel. Our *in vitro* experiments confirmed the view that none of the enzymes in the human gastrointestinal tract can hydrolyze inulin to any extent.

The exact nature of the carbohydrates in artichokes is not known. It is certain, however, that in roots which have been stored for some time carbohydrates are present which are hydrolyzable by yeast invertase and yield dextrose and fructose. Inulin itself is unaffected by invertase. According to Colin,²⁴ the carbohydrate of *Helianthus* in autumn consists solely of inulin. This is partially converted during storage into inulinides, as cynanthin and helianthin, which are hydrolyzed by yeast and intestinal enzymes and yield fructose and dextrose. Thus the administration of stored Jerusalem artichokes is not equivalent to the feeding of so much inulin.

Feeding pure inulin in doses of 100 Gm. to a fructosuric patient gave rise to no fructosuria, indicating that none was absorbed, since the absorption of as little as 1 Gm. of fructose would have caused its appearance in the urine.

SUMMARY

Three cases of essential fructosuria are reported, and metabolic studies of two are presented.

This rare anomaly is viewed as a specific, probably inborn, error of metabolism localized primarily in the liver where, we believe, a specific

²³ Bouchardat and Kulz, quoted by Neuberg in von Noorden, C. Handbuch der Pathologie des Stoffwechsels, Berlin, A. Hirschwald, 1907, vol. 2, p. 212.

²⁴ Colin. Compt. rend. Soc. de biol. **166** 305, 1918.

enzymatic deficiency exists resulting in impaired ability to fix fructose as glycogen. The metabolism of other carbohydrates is undisturbed. The relative insignificance of insulin and epinephrine in the metabolism of fructose compared with dextrose is pointed out, and the possible intermediary metabolism of sorbitol is discussed.

Dr. Harry Sobotka contributed valuable and helpful suggestions during these investigations.

Dr. B. S. Oppenheimer permitted us to publish case 1, and Dr. George Baehr, case 3.

Dr. H. S. Paine and Dr. E. Yanovsky of the Carbohydrate Division, Bureau of Chemistry and Soils, United States Department of Agriculture, supplied the fructose-free mulin used in these experiments.

NOTE.—Since this report was prepared, we have studied three additional cases of essential fructosuria, two of which occurred in brothers. This makes a total of six cases seen within one year in one institution and indicates that the metabolic anomaly is not so infrequent as one is led to expect from a study of the literature.

EFFECT OF THYROXIN AND ANTITHYROID SUBSTANCES ON THE SERUM LIPASE

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ST. PAUL

Since hyperthyroidism was first recognized, numerous investigators have attempted to discover a substance capable of inhibiting the action of the thyroid hormone. In the earlier attempts milk, meat and serum of thyroidectomized animals was used. Later serum of myxedematous persons was tried. None of these substances was capable of withstanding the critical tests of the laboratory and the clinic.

Other substances, nonspecific in character, have been reported as having a protective action against thyroxin, U.S.P., poisoning. Abelin¹ found that certain nutritional mixtures prevented the rise in the metabolic rate after injections of thyroxin. Hesse² reported the favorable action of metals, such as copper, arsenic and iron, and the waters of wells that contain these metals in prolonging the life of dogs which received daily injections of thyroxin. Certain vitamins are said to be able to a certain degree to prevent hyperthyroid manifestations.

Within the last year two new antithyroid substances from animal tissue that appear to have a definite protective action against thyroxin poisoning have been secured. Anselmino and Hoffmann³ extracted a fatty substance from the blood which they found was capable of preventing the rise in the metabolic rate in rats after the injection of thyroxin. Balo, Lovas, Bach and Neufeld⁴ found that the pancreas contained a substance which prevented the fall of serum lipase in a rabbit after the injection of thyroxin. They also found that this extract prolonged the life of the rabbit against repeated injections of thyroxin.

This study was undertaken with the object of verifying the results of Bach, Lovas and Neufeld,⁵ who found that after the injection of

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1 Abelin, I. Einfluss des Caseins auf den hyperthyroidischen Stoffwechsel, *Biochem. Ztschr.* **228** 165, 1930.

2 Hesse, E. Die Entgiftung des Schilddrüsenhormons, *Klin. Wchnschr.* **12** 1060 (July 8) 1933.

3 Anselmino, K. J., and Hoffmann, E. Darstellung, Eigenschaften und Vorkommen einer antithyroiden Schutzsubstanz aus Blut und Geweben, *Klin. Wchnschr.* **12** 99 (Jan. 21) 1933.

4 Balo, J., Lovas, L., Bach, E., and Neufeld, L. Die antagonistische Wirkung eines neuen Pankreasextraktes auf die Thyroxinvergiftung, *Arch. f. exper. Path. u. Pharmacol.* **165** 594, 1932.

5 Bach, E., Lovas, L., and Neufeld, L. Die Wirkung des Thyroxins auf die Serumlipase, *Arch. f. exper. Path. u. Pharmacol.* **165** 614, 1932.

thyroxin the blood serum lipase of a rabbit dropped in a striking manner. It was also the purpose of this study to determine whether the method was reliable and practical for the study of antithyroid substances. For this work I had at my disposal the blood extract of Anselmino and Hoffmann. In addition the possible effect of fat and insulin as antithyroid substances was investigated.

METHOD

In an investigation of the effect of various hormones on the fat-splitting ferment, Muhlbock and Kaufmann⁶ found that thyroxin regularly inhibited the action of lipase secured from the tissues. However, it had no effect on serum lipase unless the ferment was secured in a purified form. After purification, thyroxin had an inhibiting action of slight degree. A number of years ago Bauer⁷ found that the activity of the serum lipase in persons with exophthalmic goiter was markedly reduced.

With this in mind, Bach, Lovas and Neufeld injected thyroxin into rabbits and found that the serum lipase value was markedly reduced. The reduction occurred within twenty-four hours. The effect was so constant and striking that they believed that it offered an improved method for studying thyroid activity.

The lipase value is determined by the method of Rona and Michaelis,⁸ which utilizes the changes in the surface tension of a tributyrin solution as a measurement of the activity of the lipase. The split products of the lipolytic activity have practically no effect on the surface tension, which is measured by the stalagmometric method. With this method lipolytic activity is indicated by a decrease in the number of drops delivered by the instrument. The entire reaction is carried out in a buffer solution.

The rate of the lipase activity is expressed by a constant, which is derived from the logarithm of the difference of the concentration of tributyrin at the beginning and at the end of the experiment, divided by the time in minutes.

TECHNIC

A saturated solution of tributyrin is made up shortly before the test by shaking a few drops of tributyrin with a buffer solution. The buffer solution contains 1 part of monosodium dihydrogen phosphate in distilled water. This solution must be vigorously shaken for ten minutes, and then filtered twice through the same filter paper. To 5 cc of the filtrate is added 0.1 cc of the serum to be tested. Four readings are made at intervals of ten minutes. This gives the percentage of tribu-

6 Muhlbock, O., and Kaufmann, C. Die Wirkung der Hormone, insbesondere des Thyroxins auf die fettspaltenden Fermente, *Biochem Ztschr* **238** 377, 1930.

7 Bauer, J. Ueber das fettspaltende Ferment des Blutserums bei krankhaften Zuständen, *Wien klin Wchnschr* **25** 1376, 1912.

8 Rona P., and Michaelis, L. Ueber Ester und Fettspaltung im Blut und im Serum, *Biochem Ztschr* **31** 345, 1911. Bauer⁷

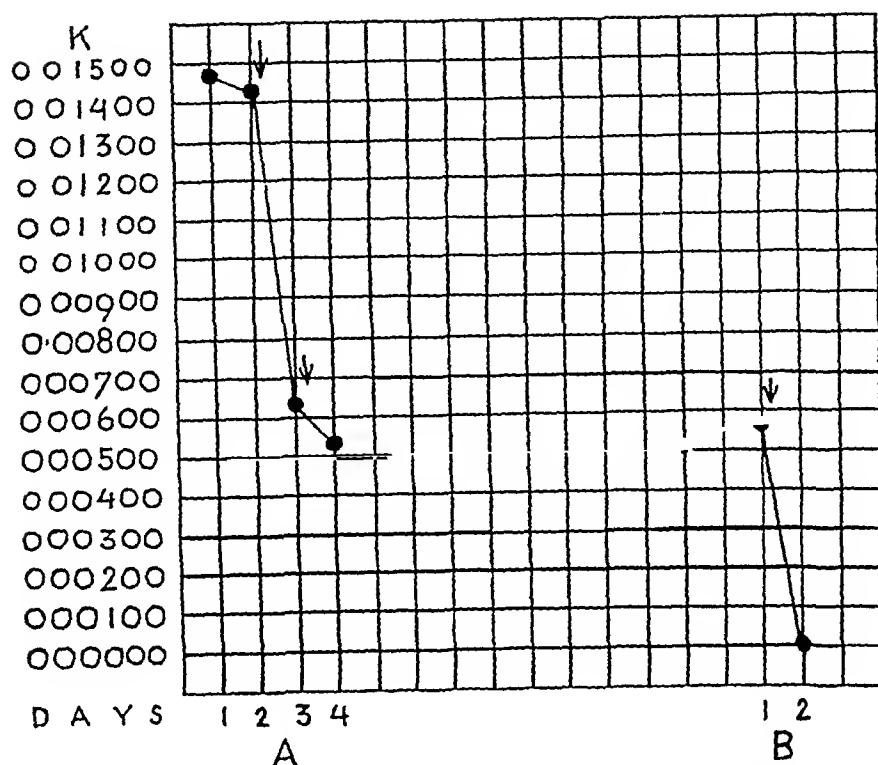


Chart 1—The effect of injections of thyroxin on the serum lipase *A*, after two injections of 0.25 mg, *B*, after a single injection of 0.5 mg. The arrows indicate the points of injection. *K* is a logarithmic figure representing the speed of the lipolytic activity. It is derived from the following formula, in which *t* represents the length of the experiment in minutes:

$$K = t \times \frac{\text{logarithm of percentage of tributyrin solution at the beginning of the experiment}}{\text{logarithm of percentage of tributyrin solution at the end of the experiment}}$$

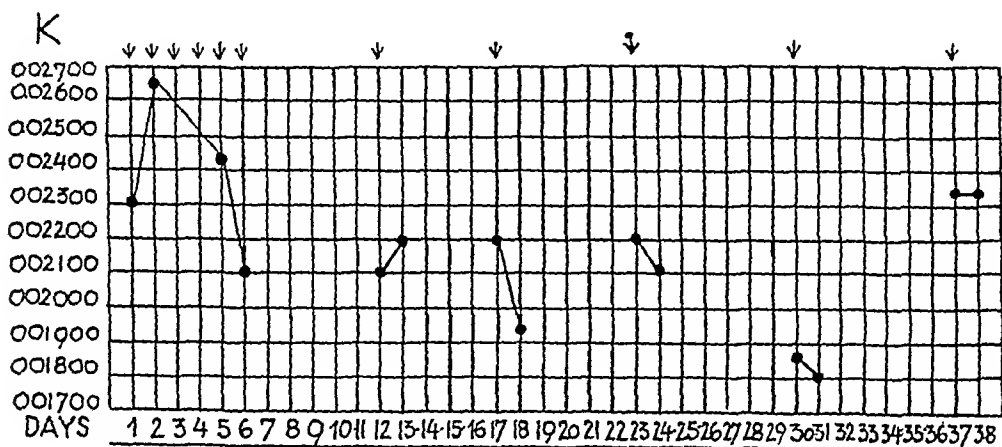


Chart 2—The effect of injections of thyroxin on the serum lipase after anti-thyroid substance was administered for seven days. The first six injections were of 0.25 mg each, and the subsequent injections of 0.5 mg each. The arrows indicate the points of injection.

tyrin present at each reading The constant is then determined by means of the following formula

$$K = \frac{t}{1} \frac{\text{Log } A}{\text{Log } A - \lambda}$$

in which t equals time in minutes, A , the per cent of tributyrin in solution at the beginning, and λ , the percentage at the successive readings

THE EFFECT OF THYROXIN ON THE SERUM LIPASE

Determinations were made on rabbits to show the effect of thyroxin on the serum lipase Chart 1 indicates the marked drop that occurred after several injections of 0.25 mg of thyroxin and one injection of 0.5 mg of thyroxin This effect is marked and occurred in every case in which the animal was not prepared with a protective substance The greatest drop almost always occurs in the first twenty-four hours Bach and his co-workers pointed out that if the injections of thyroxin are continued, the drop increases until the lipase almost disappears Shortly before the death of the animal the lipase value rises This is due to the liberation of an atoxyl-resistant lipase from the pancreas, and it probably means a severe injury to the pancreatic tissue

The constant of the activity of the lipase varies greatly for different rabbits However, in the same animal the daily variation is not great The drop following thyroxin is so marked that it cannot be confused with the slighter normal changes Bach stated the belief that within twenty-four hours with this method he could definitely determine the efficacy of antithyroid substances against thyroxin

In Animals Given Antithyroid Substance—In this group of experiments six rabbits were fed with the protective blood extract of Anselmino and Hoffmann This substance is of lipoid nature, so it was dissolved in oil and mixed with oats The rabbits were fed daily for seven days with a small amount of this mixture before thyroxin was injected

Chart 2 shows the curve after daily injections of 0.25 mg of thyroxin, this was continued for six days without producing the characteristic drop Determinations were then made at irregular intervals with 0.5 mg of thyroxin without changing the lipase value At the end of thirty-eight days the animals were still resistant to thyroxin, as demonstrated by the serum lipase

Two more rabbits were prepared in the manner described earlier The animals were given daily injections of 0.5 mg of thyroxin At the end of eleven days the serum lipase took a definite drop, but this was not so great as the drop which occurred in rabbits which did not receive antithyroid extract The injections were continued for several days, with no further change in the lipase value

All of the rabbits were given the protective extract, and all were protected against the initial drop

In Animals Fed with Fat—As the antithyroid substances are of a fatty nature and cholesterol has been reported as having an antithyroid

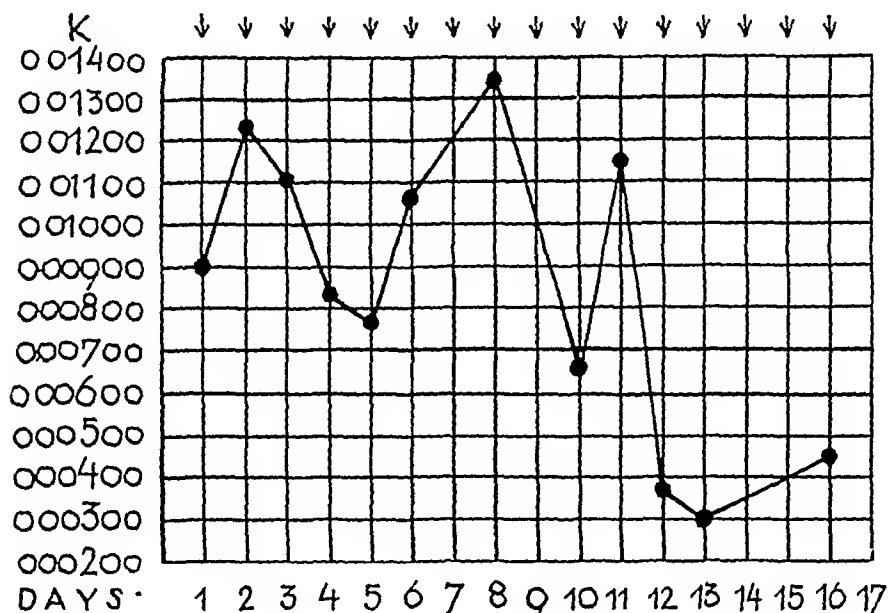


Chart 3—The same as chart 2, except that the animals received 0.5 mg of thyroxin daily

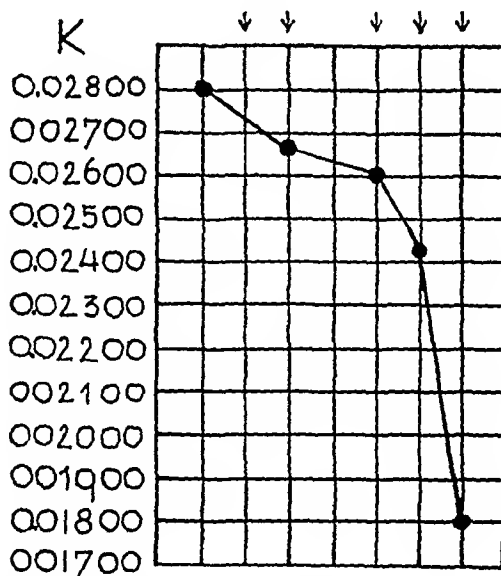


Chart 4—The effect of injections of thyroxin on the serum lipase in rabbits fed 10 cc of olive oil daily for seven days before they received thyroxin. The arrows indicate the points at which 0.5 mg of thyroxin was injected

action,⁹ I determined the effect of feeding olive oil previous to the injection of thyroxin. Two rabbits were fed with 10 cc of olive oil mixed with oats daily for ten days

⁹ Saegesser, Max. Die Schutzfunktion des Organismus bei Thyreopathie, Klin Wchnschr **12** 672 (April 29) 1933

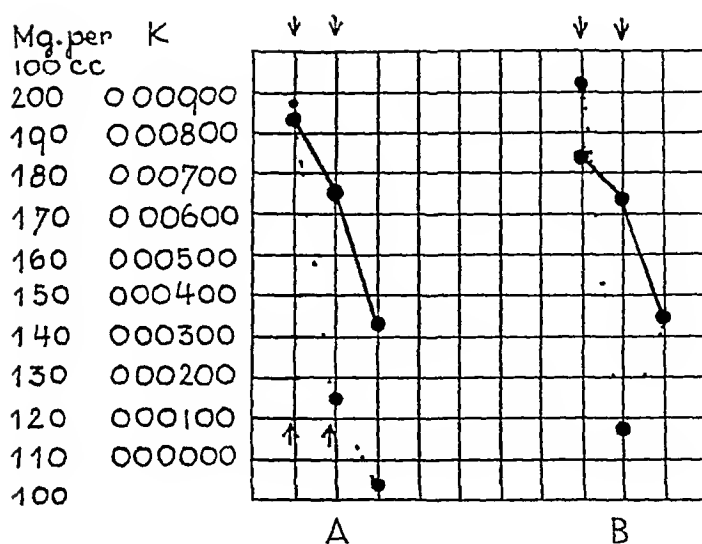


Chart 5—The effect of injections of thyroxin on the serum lipase and blood fat. The dotted line represents the curve for fat (in milligrams). The arrows indicate the points at which 0.5 was injected.

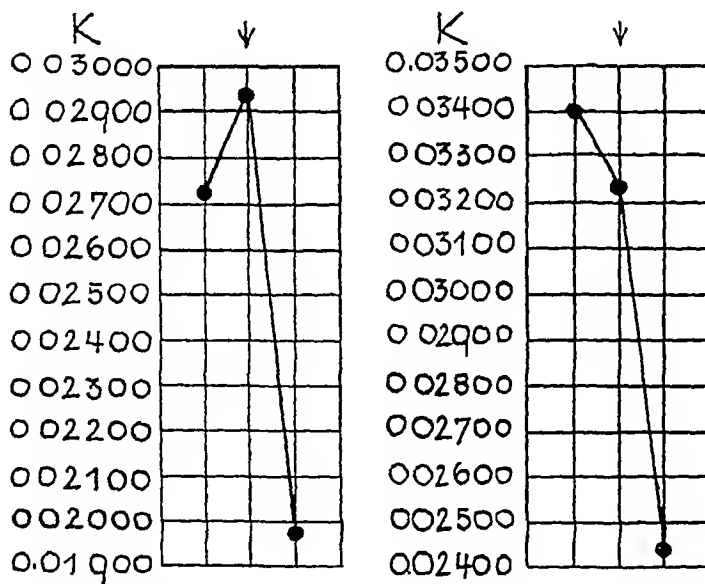


Chart 6—The effect of thyroxin on the serum lipase in a rabbit given an injection of 2 units of insulin daily for seven days before thyroxin was administered. The arrows indicate the points at which 0.5 mg of thyroxin was injected.

Chart 4 shows the lipase curve of one of them. The lipase value shows little change until the sixth day after the first injection. Five injections of 0.5 mg. of thyroxin were given.

This shows unquestionably that fat has a protective action against thyroxin. The protection, however, is not as good as that produced by Anselmino and Hoffmann's blood extract.

Various reports indicate that in hyperthyroidism there is a definite lowering of blood fat and cholesterol, and that after the injection of thyroxin in animals the blood fat is reduced. Chart 5 shows the curve of the blood fat and lipase after two injections of thyroxin of 0.5 mg. each. The method used for determining the fat was that of Rappaport and Engelberg¹⁰. In both rabbits the blood fat dropped with the fall in the lipase. In one there was a subsequent rise, while the lipase continued to fall.

In Animals Previously Treated with Injections of Insulin — Muhlbock and Kaufmann found that in vitro insulin had no effect on the serum lipase. Balo and his co-workers found that their pancreatic extract did not produce any action similar to that of insulin. Two rabbits were given 2 units of insulin daily for the purpose of causing a storage of glycogen in the liver and in that way protecting the liver against injury from thyroxin. At the end of seven days 0.5 mg. of thyroxin was injected. Chart 6 shows the sudden drop in lipase after the injection of thyroxin, which indicates that there was no protective action.

COMMENT

The determination of the lipolytic activity of the blood serum of rabbits offers an excellent method for the study of thyroid intoxication and antithyroid substances. The mechanism of this action is not known. It is conceivable that one of two things may occur after the injection of thyroxin. Either the lipase producing tissue is injured, in which case there would be a diminution in the amount of lipase in the blood serum, or the lipase itself is acted on in some manner so as to reduce its ability to split fat. Unfortunately, I do not have at my disposal an exact quantitative method for determining the amount of lipase in the blood.

All of my determinations were made on rabbits, as were those of Bach, Lovas and Neufeld. The technic is comparatively simple and permits the simultaneous investigation of a number of animals. The constancy of the normal lipase value and the marked change produced by thyroxin prevent errors in interpreting the results. In many respects it presents advantages over the older methods that are used in determining the activity of thyroxin.

¹⁰ Rappaport, F., and Engelberg, H. Eine Mikromethode zur Bestimmung des Blutfettes, Klin. Wchnschr. **11** 2080 (Dec. 10) 1932.

Although the effect of thyroxin on the lipolytic power of blood serum is only one of its many actions, the curve of the ferment's activity to split fat is a good index of what is happening to the animal. When the lipase drops almost to zero I know that if injections of thyroxin are continued, the animal will not live long. With daily injections of 0.5 mg. of thyroxin the rabbit dies usually within from six to eight days, with the lipase reaching its lowest level in from one to two days before death. With the administration of antithyroid substances, the activity of the lipase is maintained for a much longer period, but as soon as the lipase level drops other evidences of thyroid intoxication appear.

The thought then arises that perhaps the lipase itself protects the animal against thyroxin poisoning. Balo and Lovis found that their pancreatic extract *in vitro* was capable of doubling the lipase activity. I used the blood extract of Anselmino and Hoffmann, but was unable to find any increase in the lipase action *in vitro* or *in vivo*.

Fat may in some way prevent the toxic effect of thyroxin. Abelin was able to show that the loss of glycogen in the liver produced by injections of thyroxin could be prevented by the administration of fat for some time before the injection. By feeding carbohydrate alone he was not able to prevent this loss. I found that by feeding fat I could protect the lipase against thyroid intoxication, but this protection was only about half as effective as that produced by the antithyroid extracts.

If it were a question of glycogen in the liver acting to protect the lipase against thyroxin, one should get the same results with the injection of insulin. I administered insulin to two rabbits for a week before injecting thyroxin and found that there was no protective action. Anselmino and Hoffmann found that, although their substance protected the animal against a rise in metabolism, it did not prevent the loss of glycogen from the liver after the injection of thyroxin. Therefore fat must be effective in some other way than by preventing the loss of glycogen from the liver.

The question arises whether these two new animal extracts against thyroid poisoning are specific. They are composed of an antihormonal substance the action of which can be duplicated by vitamins, nutritional substances and metals. Balo and his co-workers found that their substance was present in large amounts in the pancreas, while Anselmino and Hoffmann found their substance in the pancreas in only small amounts. It is well known that substances similar in action to the so-called follicular hormone have been found in plants, and perhaps here, too, one is dealing with nonspecific substances in the form of animal extracts.

SUMMARY

1 The serum lipase of rabbits was studied after injections of thyroxin. It was found to be markedly reduced, and this action was felt to be useful in the study of antithyroid substances.

2 The blood extract of Anselmino and Hoffmann was found to have a definite action in preventing the fall of the serum lipase.

3 The feeding of olive oil also had a protective action that was only 50 per cent as effective as the blood extract.

4 Insulin injected for seven days before the injections of thyroxin did not protect the serum lipase.

5 It was felt that these substances were not specific in their action.

THROMBO-ANGIITIS OBLITERANS

IX THE CAUSE OF DEATH

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For many years after 1879, when von Winiwarter¹ first described "a peculiar type of endarteritis, endophlebitis and gangrene of the feet," little attention was paid to this form of peripheral vascular disease. Weiss² and von Manteuffel³ contributed studies of the pathologic process, but it was left for Buerger⁴ to give a detailed account of all aspects of the entity from both the clinical and the pathologic standpoint. He was the first to point out the thrombotic and inflammatory nature of the process, the involvement of veins as well as of arteries and the characteristic clinical phenomena. He incorporated all these concepts in the name which he gave to the disease, thrombo-angitis obliterans.

An extensive literature now exists on many phases of this malady. However, little is known concerning the fate and especially the mode of death of patients with this condition. Usually only transient phases of disease are observed. Fuller understanding comes with the ability to observe the extended and completed course of the pathologic processes.⁵ Judging from the paucity of published records of fatal cases and post-mortem observations, this aspect of the study of thrombo-angitis obliterans has escaped attention. Prognosis is limited to judgments about the possibility of reestablishing and compensating for an impaired circulation and to decisions concerning the ultimate amputation or conservation of the extremities. No thought has been given to the fate of the entire organism. Will other organs be involved? This and similar questions can be answered only after groups of cases have been followed

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1 von Winiwarter, F. Arch f klin Chir **23** 202, 1879

2 Weiss, E. Deutsche Ztschr f Chir **40** 1, 1895

3 von Manteuffel, Z. Arch f klin Chir **42** 569, 1891

4 Buerger, L. Am J M Sc **154** 319, 1917

5 Moschowitz, E. A Biologic Concept of Disease, J A M A **99** 714 (Aug 27) 1932

to the end. In the light of these considerations, it seems important to report the following forty-seven cases of thrombo-angitis obliterans in which there was a fatal outcome.

SELECTION OF CASES

Only undoubted cases of thrombo-angitis obliterans are included in the group. The clinical criteria include the presence in men between the ages of 20 and 45 of obliterative vascular disease in the extremities. The commonly associated symptoms of the disorder, such as coldness, change of color with a different position and intermittent claudication, were usually present in varying degree. A history of recurring phlebitis, of ulcerations of the fingers or toes, with operative or spontaneous loss of digits or amputation of the extremities at this age, gave added weight to the diagnosis of thrombo-angitis obliterans. Involvement of the upper extremities was considered particularly significant. In order to rule out combination forms, we did not include cases of peripheral vascular disease associated with diabetes, gout or syphilis. These disorders are known to hasten the development of arteriosclerosis. Hypertension militated against the inclusion of a case when it was clear that an elevated blood pressure had existed previous to the appearance of symptoms of arterial obstruction. Cases in which calcified vessels could be visualized by x-rays were excluded. Differentiation from arteriosclerotic vascular disease is difficult in patients who first present symptoms of impaired circulation between the ages of 45 and 55. Therefore, such cases were not considered in this series except in one instance in which the history and physical and pathologic examinations left no doubt about the diagnosis (case 38). In many instances examination of the vessels of an amputated extremity revealed lesions interpreted as typical of the disease confirming the clinical diagnosis.

Fulfilling these clinical diagnostic requirements were forty-seven cases, all of which terminated in death. Autopsy was performed in nineteen cases. Most of these patients were observed at some stage of their illness by one of us (S. S.).

A short clinical history of each case in which autopsy was performed with a résumé of the relevant pathologic observations follows. For the sake of brevity clinical abstracts of the cases without postmortem examination are omitted. Table 1 lists the more important features of all the cases in schematic form.

REPORT OF CASES

CASE 1—A. H., a Russian Jewish pedler, began to have pain in the left foot on walking at the age of 42. Gangrene appeared in the great toe, which sloughed off, leaving an ulcer. He smoked many cigarettes a day. For three years he received

TABLE 1—Essential Features of Forty-Seven Cases of *Thrombo-Angitis Obliterans*

Relevant Pathologic Observations												
No	Name	Sex	Age		Duration of Disease, Years	No of Limbs Involved	No of Amputations	Clinical Cause of Death	Autopsy	OPERATIVE INTERVENTION		
			Onset	Death								
1	A H	M	42	46	1	2 legs	1	Postoperative infection and toxemia	Yes		(1) Gangrene and cellulitis of amputation stump, (2) pyrenchymatous degeneration of heart, liver and kidneys, (3) no thrombosis in any major artery in the trunk	
2	W S	M	31	45	14	2 legs	1	Postoperative hemorrhage	Yes		(1) Mural thrombosis of left ventricle of heart, (2) generalized arterio sclerosis, (3) thrombosis of left common iliac artery (1) no other arterial thromboses in the abdomen	
3	D S	M	39	59	20	4	2	Postoperative spreading gun grease in stump	No		(1) Thrombotic occlusion of the left femoral artery, (2) mild arterio sclerotic changes in the iliac arteries, (3) no visceral thromboses	
4	S C	M	35	37	2	2 legs	1	Postoperative hemorrhage and infection	Yes			
5	P N	M	26.5	28	1.5	2 legs	0	Postoperative hemorrhage	No		(1) Thrombotic occlusion of both iliac arteries with ascending thrombosis into aorta up to level of renal arteries, (2) thrombo angitis obliterans of both hypogastric arteries, (3) thrombotic occlusion of both coronary arteries with myomalacia of left ventricle with forina tion of an aneurysm, (4) arteriosclerosis of aorta and both carotid, subclavian and pulmonary arteries, (5) multiple embolism of branches of pulmonary artery, (6) hyperplasia of medulla of both suprarenal glands	
6	H F	M	39	43	4	4	1	Repeated pulmonary emboli, coronary thrombosis	Yes			
7	M S	M	31	45	14	3	2	Postoperative toxemia	No			
INTERCURRENT DISEASE, ACCIDENTS, SUICIDE												
8	I G	M	29	42	13	2 legs	1	Lymphosarcoma of the small intestine	No			
9	N F	M	29	49	20	4	2	Carcinoma of the colon	Yes		(1) Carcinoma of the colon with hepatic metastases, (2) slight arterio sclerosis of the ascending aorta, (3) coronary vessels relatively normal, (4) no thromboses in the major vessels in the trunk	
10	N S	M	37.5	39	1.5	4	0	Erysipelas	No			
11	S J	M	40	45	5	4	0	Gastric carcinoma	No			
12	W S	M	32	38	6	3	0	Carcinoma of head of pancreas	Yes		(1) Small round cell sarcoma of bone or of the head of the pancreas, (2) no vascular thromboses in any of the viscera	
13	H S	M	38	42	4	3	0	Carcinoma of colon	No			
14	L C	M	34.5	42	7.5	2 legs	1	Appendicitis, postoperative uremia	No			

	H K	M	33	5	0	5	2 legs	0	Fractured skull from fall	Yes	(1) Fracture of skull with lacerations of brain, (2) no abdominal or thoracic examination
15	H K	M	33	5	0	5	2 legs	0	Fractured skull from fall	Yes	(1) Fracture of skull with lacerations of brain, (2) no abdominal or thoracic examination
16	S S	M	23	35	12	4	4	1	Suicide	No	(1) Mildly atherosclerotic coronary arteries, (2) thrombosis of branches of pulmonary artery to both lower lobes, (3) spirochetal pneumonia
17	M G	M	42	60	18	1	1	2	Postprostatectomy (1st stage)	Yes	
18	M S	M	20	27	7	1	1	2	Pulmonary infection	No	
19	J C	M	30	53	23	1	1	2	Pneumonia	No	
ASTHENIA AND CACHEXIA											
20	S S	M	29	42	13	1	1	2	Gangrene of stump with toxemia	Yes	(1) Thrombosis of abdominal aorta with complete occlusion, (2) gangrene of both lower extremities, left hip, arm, axilla and penis, (3) coronary sclerosis, (4) parenchymatous degeneration of viscera
21	T R	M	41	42	1	2	lets	1	Spreading gangrene of the stump	Yes	(1) Gangrenous wound of stump where left leg had been amputated below the knee, (2) fourth and fifth toes of right foot missing, (3) atherosclerosis of coronary vessels, (4) no arterial thromboses in the viscera
22	M S	M	30	45	15	1	1	2	Emaciation, cachexia, hypostatic pneumonia	No	
23	J M	M	38	56	18	4	4	2	Gradual cachexia, mesenteric thrombosis (?)	Yes	(1) Status after amputation of both lower extremities at mid thigh, (2) thrombosis of branch of superior mesenteric artery (thrombo aneuritis obliterans?), (3) thrombosis in right and left femoral arteries, (4) severe arteriosclerosis of coronary vessels, aorta—generalized arteriosclerosis
24	S A	M	32	43	11	1	1	2	Staple, as thenia, cerebral symptoms	No	
25	M K	M	35	51	19	2	legs	2	Myocardial insufficiency, broncho pneumonia	No	
EXTRA PERIPHERAL VASCULAR ACCIDENTS AND SUDDEN DEATH											
26	S W	M	40	47	7	2	legs	1	Sudden death	No	(1) Thrombosis in hepatic and left iliac arteries, (2) mild coronary sclerosis trophy and dilatation, (3) mild coronary sclerosis
27	M G	M	35	42	7	3	1	1	Sudden death	No	
28	H F	M	36	54	18	1	1	2	Sudden death	No	
29	H T	M	43	44	1	2	legs	0	Sudden death	No	
30	S G	M	19	28	9	1	1	2	Sudden death	No	
31	M L	M	30	41	14	2	legs	2	Angina pectoris, heart failure	Yes	
32	J B	M	32	50	18	2	legs	1	Repeated coronary occlusions	No	
33	S R	M	33	42	9	2	legs	2	Ortner's syndrome, shock	Yes	(1) Old and recent thrombi on walls of internal and external iliac arteries, (2) thrombosis in right coronary artery with myocardial infarction, (3) thrombotic occlusion of the celiac axis with extension into hepatic, splenic, cystic and pancreaticoduodenal arteries, (4) thrombotic occlusion of inferior mesenteric and superior mesenteric arteries, (5) perforations in a gangrenous ileum, (6) congestion of ascending and transverse colon

TABLE 1—*Essential Features of Forty-Seven Cases of Thrombo-Angitis Obliterans—Continued*

No	Name	Sex	Age		Dura tion of Dis- ease, Years	No of Extrem- ities In- volved	No of Ampu- tations	Clinical Cause of Death	Autopsy	Relevant Pathologic Observations
			Onset	Death						
34	H R	M	39	59	20	4	2	Myocardial in- sufficiency	No	
35	I Z	M	45	48	3	2 legs	0	Coronary throm- bosis	No	
36	L S	M	37	42	5	4	1	Myocarditis	No	
37	W S	M	39	44	5	2 legs	1	Thrombosis in cerebral artery with hemiplegia	No	
38	M P	M	47	68	21	2 legs	2	Disease of coro- nary arteries, heart failure	No	
39	A K	M	31	36	5	2 legs	1	Coronary thrombosis	No	
40	B F	M	41	49	8	2 legs	1	Coronary thrombosis	No	
41	S S	M	35	45	10	4	2	Coronary thrombosis	No	
42	M T	M	39	53	14	2 legs	1	Coronary thrombosis	Yes	(1) Coronary sclerosis with occlusion of left circumflex and anterior descending arteries, (2) recent and old infarcts of left ventricle (3) localized adherent pericardium, (4) slight generalized athero- sclerosis
43	F K	M	25 (Reported by Buerger)	27	4	2 legs	2	Coronary thrombosis	Yes	(1) Thrombosis with occlusion of left anterior descending coronary artery with recanalization (?), (2) no other vascular occlusions
44	T L	M	34 (Reported by Buerger)	39	5	4	2	Thrombosis in abdominal aorta	Yes	(1) Slight coronary atheroma, (2) thrombotic occlusion of abdominal aorta, (3) thrombosis of right renal artery
45	B D	M	18 (Reported by Buerger)	21	3	2 legs	1	Mesenteric thrombosis	Yes	(1) Marked coronary atheroma with patchy myocardial fibrosis (2) thrombosis of superior mesenteric artery, celiac axis, left internal iliac and femoral arteries, (3) gangrene of terminal 4 feet of ileum, (4) in- farcts of spleen and kidneys
46	A S	M	35	48	13	4	2	Coronary thrombosis	Yes	(1) Marked coronary sclerosis with thrombotic occlusion of left anterior descending artery (old and recent), (2) myocardial infarction (3) arteriosclerosis of aorta and renal arteries, (4) reduced lumens of external iliac and femoral arteries, (5) cerebral arteriosclerosis with thrombosis in branches of middle and anterior cerebral arteries
47	S M	M	35	56	21	4	2	Coronary thrombosis	Yes	(1) Coronary sclerosis with occlusion of left anterior descending coro- nary artery, (2) old occlusion of a branch of right coronary artery, (3) arteriosclerosis of cerebral vessels with thrombosis of lentulo- strate artery, (4) severe aortic arteriosclerosis with occluding throm- bus extending into iliac arteries

treatment of various sorts with some benefit. He was then seen in the Mount Sinai clinic for thrombo-angitis obliterans. At this time there was an ulcer 3 by 2 cm. on the stump of the left great toe. No pulsations were present in the left foot. The right anterior tibial artery was closed and the right posterior tibial artery open. The circulation in the upper extremities was normal. Under treatment the ulcer slowly diminished in size, and pulsation reappeared in the left foot. An infection developed which spread rapidly with severe constitutional symptoms. He was admitted to the Mount Sinai Hospital wards and immediate amputation was done. Pathologic examination of the amputated limb revealed thrombo-angitis obliterans with phlegmonous cellulitis. The postoperative course was stormy, and the patient succumbed to general toxemia a few days later.

Summary—In a Russian Jew, aged 45, who had thrombo-angitis obliterans for four years and who was improving with treatment, a severe infection developed requiring immediate amputation of the lower extremity. He died a few days after operation of general toxemia.

Relevant Postmortem Observations—There were gangrene and cellulitis of the stump and parenchymatous degeneration of the heart, liver and kidneys. No thrombosis was found in any major artery in the trunk.

CASE 2—W. S., an American, aged 45, began to have pain in the calves of the legs on walking at the age of 31. Numbness and burning in both feet were predominant symptoms for many years. A few months previous to admission to the Mount Sinai Hospital he had had phlebitis in the lower extremities. Soon after this the patient stubbed his right foot, following which an ulcer appeared on the right fourth toe. The fifth toe on the right foot also became discolored and swollen. He had been an excessive smoker since the age of 12. Examination revealed normal circulation in the upper extremities. Both femoral arteries and all the arteries in both lower extremities were closed. A small ulcer was present on the plantar surface of the fourth toe on the right foot. The blood pressure was 118 systolic and 94 diastolic. A roentgenogram of the lower extremities showed no calcification of the vessels. He improved with intravenous saline therapy, and was transferred to the clinic. He did not appear for a few months, and when seen had an extensive ulcer over the right ankle. Later the right lower extremity was amputated at the United States Naval Hospital in Brooklyn. He succumbed after this operation.

Summary—An American, aged 45, who had smoked for many years, had thrombo-angitis obliterans from the age of 31. He died after an amputation of the right lower extremity.

Relevant Postmortem Observations (United States Naval Hospital, Brooklyn)
—Heart and Great Vessels. "Generally speaking the precordial sac was normal. However, over the apical portion of the left ventricle there appeared to be a little loose fibrin. The right side of the heart was in a state of extreme dilatation, and the muscle of this portion of the heart was markedly deficient in tonus. Incision into the respective cardiac chambers revealed the heart generally dilated and the muscle, particularly that comprising the left ventricle, to be extensively fibrosed focally. At the apical portion in this ventricle was a mural thrombus almost the size of a golf ball which was characteristically layered by progressive organization. This thrombus had become intimately attached to the underlying endocardium, so that a line of cleavage was not discernible and separation of thrombus from cardiacum could not be effected, in fact, organization had progressed so completely that the regressive changes had undergone consummation at frequent points with calcifi-

cation The valves were essentially normal The coronary arteries were markedly sclerosed, but neither thrombosis nor embolism was discernible The aorta throughout its course showed extensive areas in which fat was deposited within the intima Of more significance, however, were numerous foci in the abdominal portion of the aorta where calcification and ulceration had resulted in extreme thrombosis, which had become so marked in the right common iliac arterial branch that virtual occlusion of the lumen here was effected by well organized clots Even in this thrombosed portion calcification had ensued"

Microscopic Examination—In the heart, "there are portrayed with significant clarity areas of widespread parenchymatous replacement by scar tissue richly infiltrated by wandering and plasma cells Pronounced degeneration of muscle is connoted by the presence within the fibers of huge amounts of fat Brown atrophy is very prominent A specific reaction to inflammation is not, however, depicted The coronary vessels show pronounced degeneration of the intima of the fatty type, with frequent regressive changes connoted by hyalinization"

In the aorta, "widespread degeneration within the intima is clearly portrayed Frequently these degenerative lesions have undergone further retrogression by changes incident to hyalinization in centers of calcification The normal continuity of the media appears to be uninterrupted"

Summary Autopsy revealed mural thrombosis of the cardiac left ventricle, generalized arteriosclerosis and thrombosis of the left common iliac artery There were no other arterial thromboses in the abdomen

CASE 4—S C, a Polish Jew, aged 37, a habitual smoker, began to have a pain in the legs at the age of 35 Four months before admission to the Mount Sinai Hospital pain in the toes of the left foot became intense, interfering with sleep A few weeks later one of the toes on the left foot became black Examination revealed a chronically ill man of 37 The heart and lungs were normal The abdominal examination gave negative results The radial arteries were pulsating and both femoral arteries were open, but all other pulsations were absent in both lower extremities A large ulcer was present over the dorsum of the left middle toe which was blue-black and obviously gangrenous Alcohol was injected into the posterior tibial nerve, with some relief from pain The musculocutaneous nerve was also resected and given an injection The gangrene affecting the left toe spread, making amputation of the left lower extremity at the lower part of the thigh necessary The stump bled a few times after the operation, and the patient succumbed to a combination of infection and exsanguination

Summary—A Jew, aged 37, who had symptoms of thrombo-angitis obliterans for two years, required amputation for relief of the pain and the spreading gangrene He succumbed after amputation to a combination of hemorrhage and infection

Relevant Postmortem Observations—Thrombotic occlusion of the left femoral artery and mild atherosclerotic changes in the iliac arteries were present There were no visceral thromboses

CASE 6—H F, a Russian Jewish salesman, aged 43, had intermittent claudication in both legs for four years Three months before admission to the Mount Sinai Hospital ulcers developed on both feet, and later on the right leg Pain became so severe that the patient became bedridden He smoked on the average twenty cigarettes a day Examination showed a severely sick, poorly nourished man The heart sounds were poor The pulse was regular The blood pressure could not be obtained because of the vascular involvement The left radial pulse was small, the left ulnar artery was closed There were no pulsations at the

right wrist and none in either lower extremity Both femoral arteries were closed The left leg was swollen and blue, and a black necrotic ulcer was present below the ankle The right foot was swollen and there were ulcers on the heel and above the ankle The temperature ranged from 101 to 105 F An amputation in the middle of the left thigh was done under general anesthesia, at which time it was noted that the femoral artery was almost completely occluded Five days after the operation, the patient expectorated bright red blood, became cyanotic and dyspneic and went into cardiac collapse In spite of energetic stimulation he died

Summary—A Russian Jew, aged 43, who had thrombo-angitis obliterans for four years, was admitted to the hospital, critically ill Amputation of an infected gangrenous leg was done He died five days after the operation in sudden cardiac collapse

Relevant Postmortem Observations—Examination revealed thrombo-angitis obliterans, thrombotic occlusion of both iliac arteries with ascending thrombosis into the aorta up to the level of the renal arteries, thrombosis of both hypogastric arteries, marked coronary sclerosis with thrombotic occlusion of the left anterior descending artery, narrowing of the right coronary artery and myocardial fibrosis, myomalacia of the left ventricle with aneurysm, atherosclerosis of the aorta and carotid subclavian and pulmonary arteries, multiple embolism of the branches of the pulmonary artery, and hyperplasia of the medulla of both suprarenal glands

CASE 9—N F, a Russian Jew, aged 49, began to have symptoms of thrombo-angitis obliterans at the age of 29 One year later, owing to the progression of the disease, amputation of one lower extremity was done at the Mount Sinai Hospital The following year the second extremity was amputated He had smoked since the age of 20 He was seen in the clinic at the age of 44 with symptoms of involvement of the hands Physical examination revealed two well healed stumps There were two atypically situated pulses at each wrist The blood pressure was 155 systolic and 100 diastolic An electrocardiogram revealed no abnormalities With the cessation of smoking and on intravenous saline therapy, the symptoms cleared up completely Gastro-intestinal symptoms appeared at the age of 49 He was readmitted to the hospital at which time study disclosed carcinoma of the hepatic flexure with metastases, from which he died Autopsy confirmed the diagnosis

Summary—A Russian Jew, who had thrombo-angitis obliterans for twenty years and who required amputation of both lower extremities, died at the age of 49 of carcinoma of the colon

Postmortem Observations—Examination revealed carcinoma of the colon with metastases to the liver and slight arteriosclerosis of the ascending aorta The coronary vessels were normal, and no thromboses were found in the major vessels of the trunk

CASE 12—W S, an Austrian Jew, aged 38, began to have pain in the right foot at the age of 32 He was an inveterate smoker Examination showed an absent radial pulse All other pulses in the upper extremities were present, as were both femoral pulses Both popliteal arteries were closed, and no pulsations were present in either foot The patient was treated with hypertonic saline solution intravenously He continued to smoke During the course of his treatment abdominal symptoms appeared He was admitted to the Mount Sinai Hospital where he eventually died Autopsy showed a widely disseminated carcinoma arising in the head of the pancreas

Summary—A man of 38, who had thrombo-angitis obliterans for six years and who on presenting himself had advanced arterial impairment in the lower extremities, died of carcinoma of the head of the pancreas with metastases

Postmortem Observations—Examination revealed small round cell sarcoma of the bone or of the head of the pancreas, with metastases to the liver, lungs and bones, and no vascular thromboses in any of the viscera

CASE 15—H K, a non-Jewish Pole, aged 33, a window cleaner, had coldness and pain in his left foot for three months. It was necessary to rest three times while walking one block. There was no history of migrating phlebitis, nor were there ever any ulcerations. He had smoked fifteen or twenty cigarettes a day since the age of 15. Examination revealed normal circulation in the upper extremities. Both femoral and popliteal arteries were pulsating, as were all the arteries in the right foot. There were no pulsations in the left foot. Smoking was prohibited and intravenous hypertonic saline injections were given three times a week. He continued to show further improvement under treatment. While at work, the patient fell from a six story window and died of a fractured skull. An incomplete autopsy was done by the medical examiner.

Summary—A non-Jewish Pole, aged 33, began to have symptoms of thrombo-angitis obliterans. When smoking was discontinued and hypertonic saline solution was administered intravenously, he improved considerably and was able to resume his former occupation of window cleaner. While at work he fell from a six story window and died of the resulting injuries. A complete autopsy was not done. Postmortem examination confirmed the cause of death as fracture of the skull with multiple lacerations of the brain. The abdominal or thoracic viscera were not examined.

CASE 17—M G, a Russian Jewish operator, had phlebitis about the left ankle at the age of 42. A year later there was pain in the fingers of the right hand. This finally disappeared. About four and one-half years before his admission to the Montefiore Hospital gangrene developed in the right foot requiring an amputation of the right lower extremity at the middle of the thigh. Three years later amputation of the left lower extremity at the middle of the thigh was done for gangrene of the toes. Gangrene of the fingers of both hands was present at the time of admission. The patient smoked ten cigarettes a day. Examination revealed emphysema and some basal pulmonary râles. The heart was normal, the blood pressure was 130 systolic and 84 diastolic. Both lower extremities had been amputated. The left radial pulse was smaller than the right. During the ten years of his stay in the hospital he felt well. At the age of 60, urinary symptoms developed. Prostatectomy was attempted. He died of pulmonary infection postoperatively.

Summary—A Russian Jew, who had thrombo-angitis obliterans beginning at the age of 42 and who had both lower extremities amputated, besides suffering gangrenous involvement of many of the digits of both hands, died at the age of 60 of a postoperative (prostatectomy) pulmonary infection.

Relevant Postmortem Observations—Autopsy revealed patent coronary arteries, mildly atherosclerotic, spirochetal pneumonia of both lower lobes with formation of cavities, thrombosis of the pulmonary arteries to both lower lobes, no other vascular occlusions, and no significant microscopic changes.

CASE 20—S S, an Austrian Jew, had intermittent claudication for eight years, beginning at the age of 29. Amputation of the left great toe had been done, and ulceration persisted. He was a moderate smoker. Examination at the Mount Sinai clinic showed all vessels closed in both feet and gangrenous ulceration of

the left foot. In spite of treatment the gangrene progressed and an amputation of the left lower extremity was done at the middle of the thigh. One year later, because of similar involvement of the right foot, amputation was done at the Montefiore Hospital. Examination of this specimen pathologically showed the usual lesions of thrombo-angitis obliterans. He was seen several times during the next three years, and presented ulcerations of two fingers of his right hand. At this time a spreading gangrene of the right stump developed and he died. The patient refused to stop smoking throughout his entire illness.

Summary—An Austrian Jew who had thrombo-angitis obliterans for thirteen years, beginning at the age of 29, and who had had amputations of both lower extremities and also involvement of both upper extremities, died of a spreading gangrene of the right stump.

Relevant Postmortem Observations—Heart. The coronary arteries were straight and soft. The myocardium was pale, tan and flabby in consistency. Both ventricles were hypertrophied and dilated. The valves were normal. The anterior descending branch of the left coronary artery was occluded by a greenish-white mass. Other coronary arteries showed slight atherosclerosis, but were everywhere patent.

Vessels. The abdominal aorta was completely occluded by a grayish thrombus below the renal arteries. This manifestation extended into the common iliac vessels where the thrombus became red. The upper portion of the abdominal aorta had a marked "tree bark" appearance. The right femoral artery was occluded at one point near its origin by yellowish-gray material. The left femoral artery showed no abnormalities, nor did the renal, carotid, left brachial or mesenteric arteries. The inferior vena cava showed no abnormalities.

Microscopic Examination. The coronary artery showed occlusion, organization and recanalization, the vein was uninvolved. Of three sections of the right femoral artery one was negative, though an adjacent vein had been completely replaced and recanalized. A second section showed moderate intimal proliferation with a thrombus undergoing organization, and adjacent veins had been occluded and recanalized. A third section was completely occluded by a thrombus, most of which was fairly recent, and a branch had been completely occluded and recanalized. In the left femoral artery, at one point, there was considerable intimal proliferation, but the lumen remained patent. The wall of the vein showed collections of lymphocytes. The artery had been occluded and recanalized.

Summary. Autopsy revealed thrombo-angitis obliterans, thrombosis of the abdominal aorta with complete occlusion, gangrene of both lower extremities, the left hip, the left arm, the axilla and the penis and coronary sclerosis, with thrombosis and recanalization of the left anterior descending coronary artery.

CASE 21—T. R., a Russian Jew, aged 42, first began to have severe pain and paresthesia in his left leg one year before admission to the Mount Sinai Hospital. The toes on this foot became gangrenous and separated spontaneously. Four months later the foot was amputated at the ankle at the Johns Hopkins Hospital. Two weeks before admission to the Mount Sinai Hospital, pain occurred in the left thigh. The patient had smoked from twenty to forty cigarettes a day for many years. Examination revealed a chronically ill, emaciated man with emphysema of the lungs and a normal heart. At the site of the amputation of the left foot there was a gangrenous wound. On the inner aspect of the distal third of the left thigh was a swollen, red, tender elevation, exuding pus. The fourth and fifth toes of the right foot were not present. The left femoral pulse was small, the right femoral pulse was present and the right popliteal pulse was small. There were

no pulsations in the right foot. At no time was the patient in a condition to undergo amputation. In spite of transfusions and supportive treatment he gradually lost ground and died of spreading gangrene four weeks after admission.

Summary—A man of 42, who had had symptoms of thrombo-angitis obliterans in both lower extremities, which had required amputation of his left foot, died of spreading gangrene from this unhealed wound.

Relevant Postmortem Observations—Examination revealed a gangrenous wound of the stump of the left leg, which had been amputated below the knee. The fourth and fifth toes of the right foot were missing. Vessels in the stump showed the changes characteristic of thrombo-angitis obliterans. The heart was small, and the muscle was brown and thinned. The coronary orifices and arteries were patent. There was some atherosclerotic thickening of the right coronary artery. Aside from evidence of cachexia, the other organs presented no abnormalities. There were no arterial thromboses.

CASE 23—J. M., a Russian Jewish driver, aged 47, was seen at the Montefiore Hospital. Nine years previously he had had an amputation high in the thigh for thrombo-angitis obliterans. He was admitted because for the previous eight years he had had constantly recurring pain and ulcerations of the other leg. He smoked moderately. Physical examination showed a thin, middle-aged man. The heart and lungs were normal. The stump was well healed. The left lower extremity was atrophic and the foot was discolored. The blood pressure was 140 systolic and 80 diastolic. There were no pulsations in the foot. Shortly after admission, because of the progression of symptoms, an amputation of the left extremity at the middle of the thigh was done. Pathologic examination of this amputated extremity revealed the typical lesions of thrombo-angitis obliterans. The patient persisted in smoking in spite of advice. His further course was characterized by progressive involvement of the fingers of the right hand. At this time one artery was closed in each wrist. The right index finger finally sloughed off. Then he had attacks of colicky abdominal pain, accompanied by bloody diarrhea, vomiting and tenesmus. There was tenderness in the epigastrium and lower quadrant on the right side, but no rigidity or fever. It was suspected, but never definitely established clinically, that the patient had mesenteric arterial involvement. His course was rapidly downhill, and shortly before his death, at the age of 56, he became irrational.

Summary—A Russian Jew had his first amputation for thrombo-angitis obliterans at the age of 38, and his second amputation at 47. There was subsequent involvement of both remaining extremities with clinical evidence of mesenteric arterial occlusion. He died at the age of 56.

Relevant Postmortem Observations—Examination revealed an emaciated cadaver with two stumps at the thigh and a missing right index finger. The heart weighed 190 Gm. The valves were normal and the coronary arteries were beaded and tortuous owing to atherosclerosis. The lumen of the left anterior descending artery was narrowed, but not completely occluded. No thromboses existed. The aorta showed marked arteriosclerosis extending down into the common iliac arteries. There were arteriosclerotic ulcerations and raised plaques. Both femoral vessels were completely occluded by thrombi. The renal artery showed slight arteriosclerosis. One of the smaller branches of the superior mesenteric artery was completely occluded for about 1 inch (2.5 cm.) by a red thrombus. The pulmonary artery showed atheromatosis. The inferior vena cava was normal. The abdominal viscera were normal.

Microscopic examination revealed interstitial myocardial fibrosis of the cardiac muscle. The right femoral artery and vein showed an irregularity of architecture.

Both vessels were definitely thrombotic, the arterial thrombus being composed of red and white cells and fibroblasts. Small vasa vasorum were seen outside the thrombus, there was a large amount of fibrous tissue growing irregularly into the intima and media. In another section the thrombus was composed of fibrous tissue and fibroblasts with an apparently homogeneous, structureless hyaline layer around it. The thrombus had been canalized and recanalized. The vein showed marked narrowing of the lumen by an invagination of the intima with marked narrowing of the lumen.

The process in the left femoral artery was similar to that in the right. The thrombus left only a small slit for a lumen. Canalization had evidently taken place repeatedly. There were small lumens scattered all through the thrombus. In the mesenteric artery the intima showed a good deal of thickening by a wavy hyaline structure containing numerous fibroblasts, which had markedly encroached on the lumen. Another section of this vessel showed advanced obliteration of the lumen by a thrombus which had been recanalized. Numerous young blood vessels were seen to break up the thrombus. Other small vessels appeared only as masses of fibrous tissue due to closure of their ostia. The cerebral vessels revealed arteriosclerosis.

Summary Autopsy revealed thrombo-angitis obliterans with amputation at the middle of both thighs, thrombosis of the right and left femoral arteries with thrombosis of the branch of the superior mesenteric artery (thrombo-angitis obliterans?), generalized arteriosclerosis and marked arteriosclerosis of the aorta and coronary vessels.

CASE 31—M. L., a Russian Jewish operator, first had symptoms of thrombo-angitis obliterans at the age of 30. Three years later his right lower extremity was amputated. The condition involved the other lower extremity and progressed, requiring amputation of the left leg five years later. The patient was 38 at this time, and had a blood pressure of 104 systolic and 68 diastolic. For three years he was relatively well. At the age of 41, there first appeared attacks of precordial pain, dyspnea, sweating and weakness. Subsequently dyspnea on exertion and edema of the stumps developed. Admitted to the Montefiore Hospital because of these symptoms, physical examination showed a chronically ill man of 43, with dyspnea and orthopnea. There were edema of both stumps, an enlarged heart, systolic basal murmurs and an enlarged liver. The blood pressure was 232 systolic 130 diastolic, 182 systolic, 118 diastolic, and 190 systolic and 120 diastolic. A roentgenogram showed an enlarged heart and fluid in both pleurae. The electrocardiogram revealed left ventricular predominance, notched P waves, peaked and notched QRS complexes, with low T I and inverted T III waves, and was interpreted as indicating myocardial damage. The heart failure increased, and the patient died of pulmonary edema.

Summary—A Russian Jew, who had thrombo-angitis obliterans from the age of 30, and who had amputations of both lower extremities at the ages of 33 and 38, respectively, had a hypertension and angina pectoris during the last few years of his life, and died of heart failure at the age of 44.

Relevant Postmortem Observations—The heart showed hypertrophy and dilatation but no valvular abnormalities. The myocardium was firm and grossly normal. The coronary arteries were normal, except for scattered small atheromatous plaques. The liver revealed thrombosis of the hepatic artery extending into the right and left branches, the celiac axis and its other branches were thickened but not occluded. There was atheromatous involvement in the aorta from root to bifurcation. In the terminal portion of the iliac and proximal portion

of the femoral arteries, there was an occluding thrombus which was breaking down. There were no thrombi in the right iliac artery. The vena cava and tributaries were normal.

Microscopic examination revealed moderate fatty infiltration of muscle fibers in the myocardium. The aorta showed marked intimal fibrosis and hyalinization and congestion of the vasa vasorum. The iliac artery revealed marked hyaline and fibrous thickening of intima. There was unclotted blood in the lumen. In the hepatic artery perivascular round cell infiltration and fibrosis were evident, and the lumen was filled with a laminated clot, showing organization at the periphery. Another section showed complete occlusion by a recanalized organized thrombus.

Summary Autopsy revealed cardiac hypertrophy and dilatation, thrombosis of the hepatic and left iliac arteries and mild atheroma of the coronary arteries.

CASE 33—S. R., a Russian Jewish operator, aged 42, had had thrombo-angitis obliterans for nine years. Seven years before admission his left foot had been amputated at the ankle and five years later the right leg had been removed below the knee. The clinical diagnosis of thrombo-angitis obliterans was confirmed by examination of an amputated limb. He smoked about twenty cigarettes a day. Beginning seven months before admission to the Mount Sinai Hospital, postprandial epigastric and periumbilical pain occurred without associated symptoms. The pain was colicky and was relieved by pressure on the abdomen or the application of heat. Increasing frequency and severity of these abdominal symptoms caused him to enter the hospital. Examination revealed normal circulation in the upper extremities. The pulsations in the left lower extremity, iliac and femoral arteries were small. The right external iliac, the right femoral and both popliteal arteries were closed. The stumps were well healed, but cold. The abdomen was held voluntarily rigid, making accurate examination difficult. The patient was afebrile, the blood pressure was 132 systolic and 85 diastolic. Roentgenograms of the gastro-intestinal region revealed no organic lesion of the stomach or duodenum, but showed what was interpreted as a partial obstruction in the small intestine. The abdominal pain became more constant and severe, at times requiring chloroform anesthesia for relief. In a few days the patient died of exhaustion and shock. Clinical diagnosis was thrombo-angitis obliterans with dysbasia intermittens arteria mesenterica (Ortner).

Summary—A Russian Jew, aged 42, had thrombo-angitis obliterans for nine years, during which time amputation of both lower extremities was done. For seven months before death he had recurring attacks of postprandial colic which was diagnosed as due to progressive occlusion of the vascular supply of the upper gastro-intestinal tract. He died a few days after admission from shock.

Relevant Postmortem Observations (Dr. C. Rabin)—Examination revealed well healed stumps of the left leg amputated at the tarsometatarsal junctions and of the right leg amputated below the knee. The heart weighed 300 Gm. There was an apical myocardial scar, and thrombosis in a branch of the right coronary artery had occurred. Some atheroma of the sinuses of Valsalva was present. Then the aorta was fairly free up to the origin of the celiac axis. The opening of the celiac axis was indicated by a circular depressed area of fibrosis. It was not patent. The opening of the inferior mesenteric artery also was plugged with a thrombus, completely occluding the mouth of the vessel which was thickened by an old inflammatory process. Orifices of the renal artery were widely patent. The aortic wall below the celiac axis was thin, slightly narrowed and scarred. The scars were depressed, some were stellate and mostly parallel, giving a wrinkled appear-

ance There was a slight atheromatous process in this region The common iliac vessels showed little change Both external and internal iliac arteries showed thickening of the arterial walls with thrombi—some organized and others fresh Within a few inches of the bifurcation of the common iliac arteries these vessels were very narrow, having been completely occluded by fresh and old thromboses

At the junction of the hepatic, gastric and splenic vessels the celiac axis was completely obliterated by an organized process The gastric artery appeared patent The splenic artery was thrombosed for a short distance About 3 cm from its entrance into the celiac axis it suddenly became wide and was patent all the way to the hilus of the spleen The hepatic artery from about 1 inch from the celiac axis showed numerous areas of thrombosis The lumen of the artery was narrowed and was represented by a number of recanalized channels The cystic artery showed the same condition The superior pancreaticoduodenal artery was completely closed off by a fresh thrombus The superior mesenteric artery was closed off at its mouth by a fresh thrombus Then for a distance of 2 cm it showed no change The opening of the inferior pancreaticoduodenal artery was free Farther along in its course it was occluded by an old thrombus and partly recanalized The intestinal branches of the inferior mesenteric artery were patent The main body of the artery in its course in the mesentery was completely thrombosed, mainly organized, but in some places a fresh thrombus could be discovered The wall was much thickened No free lumen could be discovered all the way to its entrance into the aorta No evidence of its opening into the aorta could be found

In the gastro-intestinal tract the upper jejunum and duodenum were normal in appearance The lower portion of the jejunum, the entire ileum and the ascending and transverse colon were deep red, the serosa was dull and opaque On the surface were numerous areas of gangrene which were more marked on the mucous membrane In two places in the ileum there were perforations from which bloody grumous intestinal contents entered the peritoneal cavity The descending colon, for the most part, showed only congestion Mesenteric veins near the intestine were dilated and well filled with a postmortem clot The vena cava and portal vein, as well as the veins of the spleen, were normal

Microscopic Examination The celiac axis was completely occluded by an organized thrombus which was partially recanalized The internal elastic membrane was clear and showed little alteration There were a number of cells containing iron pigment at the edges of the organized thrombus At one small point there was thickening in the intima with some proliferation of the elastica intima Another section of this artery showed occlusion by an organized recanalized thrombus There were no intimal or internal elastic changes The superior mesenteric artery was occluded by an old thrombus, recanalized Some intimal thickening was evident, with proliferation of the elastic tissue The media showed some lymphocytic infiltration, and the adventitia some fibrous thickening The inferior mesenteric artery was completely occluded by an organized thrombus There was no intimal thickening or changes in the elastica interna The splenic, hepatic, pancreaticoduodenal, internal and external and iliac arteries showed organized recanalized thrombosis with occasional intimal thickening or lamellation of the elastica interna

Summary Old and recent thrombi were evident on the walls of the internal and external iliac arteries There was thrombosis of the right coronary artery with myocardial scarring, and thrombotic occlusion of the celiac axis with extension into the hepatic, splenic, cystic and pancreaticoduodenal arteries There were

thrombotic occlusion of the inferior mesenteric and superior mesenteric arteries, perforations in the gangrenous ileum and congestion of the ascending and transverse colon

CASE 42—M T, an Austrian Jewish tailor, aged 53, was seen in the Montefiore Hospital. He had had vascular disease necessitating amputation of the left lower extremity at the middle of the thigh, at the age of 39. At the age of 47, he had hemiparesis, of short duration. A short time before admission to the hospital, intermittent claudication of the right leg developed. He had smoked twenty cigarettes a day for many years. Examination disclosed a well nourished man on crutches. The heart and lungs showed no obvious abnormalities. The blood pressure was 115 systolic and 75 diastolic. There were no residual neurologic signs of the previous hemiparesis. The Wassermann reaction of the blood was negative. While under observation an acute episode developed, characterized by collapse, falling blood pressure, rapid pulse, fever, cyanosis and the appearance of a pericardial rub. The patient died during this attack, which was interpreted as a coronary closure.

Summary—An Austrian Jew, who had thrombo-angitis obliterans since the age of 39, and who had an amputation of one lower extremity at that time, subsequently had temporary hemiparesis and later died in an attack of coronary thrombosis.

Relevant Postmortem Observations—In the heart and coronary arteries, recent and old myocardial infarctions were found in the left ventricular wall with a fresh mural thrombus. The left descending coronary artery branch was calcified and finally completely closed at about its middle. The circumflex artery was also occluded at about the middle. The right coronary artery was atheromatous, but not visibly occluded. The aorta and the branches were the seat of a moderately advanced atherosclerotic process.

Microscopic Examination The left iliac artery was markedly fibrous, with hyaline thickening of the intima, and the right iliac artery showed slight thickening of the media and intima. There was no stenosis or occlusion. In the pulmonary artery there was fatty and fibrous thickening of the intima, while the coronary artery showed marked fibrous thickening and slight fatty infiltration of the intima. The underlying layers were almost completely replaced by organizing scars, and underneath this zone were large areas of recent necrosis. In the aorta were small areas of fibrosis and hyalinization, with a slight tendency to calcification of the media and intima.

Summary Examination at autopsy revealed coronary sclerosis and occlusion, recent and old infarcts of the left ventricular myocardium, a localized adherent pericardium, slight generalized atherosclerosis and atheroma of the pulmonary vessels.

CASE 43 (reported by Buerger)—F K, aged 24, gave a history of having had pain in the left great toe the year before admission. The pain recurred two weeks before admission to the Mount Sinai Hospital. The toe became discolored and the foot swollen. There also were intermittent cramplike pains in the calf of the right leg on walking. Examination disclosed absence of pulsation in the left dorsalis pedis artery. The right dorsalis pedis artery pulsated. During the next three years, because of progressive occlusion of the vessels of the lower extremities, amputation of both lower extremities became necessary. Pathologic study established the diagnosis of thrombo-angitis obliterans. The patient was found dead one day, just after he had been seen alive by one of the hospital attendants.

Summary—A man, aged 27, died suddenly. He had thrombo-angitis obliterans for four years, during which period amputation of both lower extremities was done.

Relevant Postmortem Observations—The cardiac muscles were brown, with many yellow areas of degeneration and fibrosis. About 1.5 cm from the origin the lumen of the left anterior descending coronary artery was filled with a fibrous, yellowish-white substance, adherent to the wall and dividing the lumen of the vessel into two small parts (recanalization?). The right coronary artery was normal. There were no other vascular occlusions. Microscopic examination revealed the typical picture of arteriosclerosis. There was no evidence of thrombo-angitis obliterans.

CASE 44 (reported by Buerger)—T. L. began to have pain in the left foot at the age of 34. Gangrene of the toes developed, and an ulcer appeared on the dorsum of this foot. A year later the left leg was amputated at the middle of the thigh. In another year, because of involvement of the right lower extremity, amputation of this leg was done likewise through the middle of the thigh. Examination of the amputated extremities showed old and acute lesions of thrombo-angitis obliterans. Two years later, at the age of 38, he began to complain of trouble in his right hand. Examination revealed an atrophic hand with thickened skin. The brachial artery could be felt as a nonpulsating cord, and the ulnar and radial arteries did not pulsate at either wrist. Both femoral pulses were absent. Although the process in the hands did not progress, in two years the patient was again observed in the hospital because of ulceration and a slough on the stump of the left leg. Asthenia, cachexia, fever and coma ushered in the final fatal stage.

Summary—A man who had his first symptoms of thrombo-angitis obliterans at the age of 34 had progressive involvement of all four extremities, requiring amputation of both legs. He died at the age of 40 of cachexia and toxemia resulting from a gangrenous infected stump.

Relevant Postmortem Observations—Examination revealed slight coronary atheroma, thrombotic occlusion of the abdominal aorta and narrowing of the right renal artery. Microscopically the aorta and renal vessels showed arteriosclerosis with bland thrombosis and organization.

CASE 45 (reported by Buerger)—B. D., a man of 21 years, with thrombo-angitis obliterans, had an amputation through the left thigh. A few days later he experienced extreme abdominal pain with rigidity of the abdominal wall. Operation confirmed the diagnosis of mesenteric thrombosis with gangrene of the intestines. The patient died.

Relevant Postmortem Observations—Examination revealed marked coronary atheroma, patchy myocardial fibrosis, mural thrombi on a sclerotic aorta, thrombosis of the superior mesenteric artery, celiac axis and left internal iliac and femoral arteries, gangrene of the terminal 4 feet (121 cm) of ileum, and infarcts of the spleen and kidneys. Microscopically various involved vessels showed typical lesions of arteriosclerosis with thromboses. There were no lesions characteristic of thrombo-angitis obliterans.

CASE 46—A. S., a Russian Jewish operator, required amputation of a finger of the left hand because of pain and gangrene at the age of 35. A few months later some fingers on the right hand became involved. The left great toe was affected and was removed surgically. One year before admission to the Montefiore Hospital gangrene developed in the right great toe making amputation of the right

lower extremity necessary. Six months later the left lower extremity was amputated at the knee joint. The patient smoked fifteen cigars a day. Examination revealed amputation of the index and middle fingers of the right hand, the index finger of the left hand and both lower extremities. No pulse was felt at the left wrist, the right ulnar pulse was small, and the radial pulse absent. The blood pressure was 90 systolic and 50 diastolic. In the hospital the patient was comfortable. At the age of 47, he had a hemiplegic stroke, from which he recovered. A year later, while watching a baseball game he suddenly became unconscious and died an hour later.

Summary—A Russian Jew, who had thrombo-angitis obliterans for thirteen years, beginning at the age of 35, and who had amputation of numerous digits of both hands and of both lower extremities, died suddenly at the age of 48. A year before his death he had had right hemiplegia.

Relevant Postmortem Observations—Examination revealed marked coronary sclerosis, with the left anterior descending artery occluded by reddish-gray translucent material (old and recent closure), myocardial infarction, arteriosclerosis of the aorta and renal arteries, small internal iliac and femoral arteries, with greatly reduced lumens, cerebral arteriosclerosis with multiple areas of softening in the brain, and thrombosis of the branches of the middle and anterior cerebral arteries.

Microscopic examination of the arteries revealed a fresh blood and fibrin thrombosis of the coronary arteries with beginning organization and the ingrowth of fibroblasts and small blood vessels, thickening of the media and intima with hyalinization and an organized thrombus with hyalinization. In the cerebral arteries arteriosclerosis with thrombosis of the middle and anterior cerebral vessels was evident.

CASE 47—S. M., a Russian Jewish glazier, first had pain in the lower extremities at the age of 35. An infection under the right great toe nail was present at this time. This finally healed, but two years later a more extensive involvement of the left foot occurred. This finally made amputation of the left lower extremity necessary at the age of 37. Three years later repeated and spreading ulceration on the right foot resulted in amputation of the right lower extremity. On numerous occasions there were ulcerations on the fingers of the right hand. A few months before his admission to the Montefiore Hospital sugar was discovered in the urine. It had not been present at the time of the first amputation. Examination revealed the absence of both lower extremities. The right radial pulse was absent, and the right brachial pulse was small. The left radial pulse was present. During his stay in the hospital he was comparatively well. One day before his sudden death, he complained of precordial oppression.

Summary—A Russian Jew, who had thrombo-angitis obliterans since the age of 35, required the amputation of both lower extremities. There was involvement of the upper extremities also. Sugar was noted in his urine for the first time when he was 50. He died suddenly, having complained of precordial distress a day before.

Relevant Postmortem Observations—Examination revealed hypertrophy and dilatation of the heart, with myocardial fibrosis, arteriosclerosis of the coronary arteries with occlusion of the left anterior descending artery, old occlusion of a branch of the right coronary artery, cerebral arteriosclerosis, with thrombosis of the lenticulostriate artery, severe aortic arteriosclerosis, with occluding thrombus extending into the iliac arteries, and no visceral vascular thromboses. Micro-

scopically the coronary vessels revealed marked thickening of the intima and media with cellular infiltration composed of connective tissue and round cells. The lumen was narrowed and contained an adherent fresh fibrin thrombus. Marked arteriosclerosis with intimal and medial thickening was evident in the aorta.

EXTREMITIES INVOLVED, AMPUTATIONS

Twenty-two patients, or roughly one half of the total, had involvement of the lower extremities only, while the remaining twenty-five had involvement of the upper extremities also, that is to say, all patients had disease of the lower extremities, whereas none had disease only of the upper extremities.

All except eight of the forty-seven patients had undergone at least one major amputation. In the last decade the therapeutic management of thrombo-angitis obliterans has become radically altered. More successful methods of treatment and the employment of newer methods for the alleviation of pain in involved extremities have made it possible to prevent early amputation of the extremities in moderately advanced cases—heretofore a common occurrence. Today all workers in the field of therapy (Silbert,⁶ Brown and Allen,⁷ Samuels⁸ and Schlesinger⁹) have advised against an early radical operation. At the Mount Sinai Hospital amputation for thrombo-angitis obliterans in the past ten years has been reduced to a fraction of its former incidence. It may safely be predicted that in a similar group reported ten years from now the incidence of amputation will be still less.

AGE OF INCIDENCE AND DURATION OF DISEASE

Although age was considered one of the criteria for the inclusion of a case in this series, all other features of the disease in the cases reported here confirmed the diagnosis. Therefore, the analysis of the age of onset, the duration of the disease and the age at the time of death can afford some valid information. Table 2 shows the incidence for each decade.

The greatest number of cases appeared in the fourth decade of life. When it is understood that hand in hand with the occlusive process there arises an extensive collateral and compensatory vascular network

6 Silbert, S. A New Method for Treatment of Thrombo-Angitis Obliterans, *J A M A* **79** 1765 (Nov 18) 1922, The Treatment of Thrombo-Angitis Obliterans, *ibid* **86** 1759 (June 5) 1926, Thrombo-Angitis Obliterans (Buerger), *ibid* **94** 1730 (May 31) 1930.

7 Brown, G. E., and Allen, E. V. Thrombo-Angitis Obliterans, Philadelphia, W. B. Saunders Company, 1928.

8 Samuels, S. Treatment of Gangrene Due to Thrombo-Angitis Obliterans, *J A M A* **96** 751 (March 7) 1931.

9 Schlesinger, H. *Klin Wchmschr* **45** 2112, 1930.

which postpones the appearance of symptoms, it can be said that thrombo-angitis obliterans probably has its beginning most frequently in the third decade

The duration of life in three of the nine patients who began to show symptoms between the age of 18 and 30 did not exceed four years. This exaggerates the gravity of the prognosis in these persons, for there are many afflicted at this age who do very well, and because of that fact would not appear in this group. Yet these few cases would seem to indicate that not infrequently cases in which the disease appears early in life have a different character from the usual instances. The involvement is more extensive, the thrombotic feature is prominent and the general pace of the disease is accelerated. An example of this type of case was observed recently in the wards of the Mount Sinai Hospital. A man of 20 who had had symptoms for only a few months was found to have involvement of all four extremities. In one leg

TABLE 2—*Incidence of Disease by Age*

	Age of Onset (by History)			
	15 to 19	20 to 29	30 to 39	40 to 49
Number of cases	2	7	29	9

the process had advanced so far that in spite of active therapy amputation was necessary because of spreading gangrene.

In the older group, with onset between 40 and 50, comprising nine cases, the duration of life was short, except in two patients, who survived for twenty-one and eighteen years, respectively. Subjects who come under observation at this period frequently have arteriosclerosis. In other instances, because of the long though silent existence of the disease, the involvement is extensive. Frequently when patients in this group are first seen surgical procedures are necessary, but not well borne. Such circumstances accounted for the death of two of our patients (cases 1 and 21). It is to be noted that three patients in this group died of coronary thrombosis (cases 35, 38 and 40), a not uncommon mode of termination in thrombo-angitis obliterans, as will be shown later.

The twenty-nine patients who showed the first symptoms between the ages of 30 and 39 make up the largest group. Thirteen lived less than ten years after the onset of symptoms and the other sixteen survived for from ten to twenty-three years. No patient in this group lived to the age of 60. The average duration of life was 12.5 years from the onset of symptoms. This figure possesses the limitations of all "averages." It does not apply to a particular case. Perhaps the

only warranted conclusion to be drawn from the figures is that a patient presenting the first symptoms between the ages of 30 and 40 has a maximum life expectancy of roughly twenty years¹⁰

From a study of these forty-seven cases it appears that when thrombo-angitis obliterans occurs in the second or early third decade of life, it may run a stormy course, characterized by extensive thromboses and complications requiring surgical measures, with then attendant risks. This parallels many well known examples of the marked severity of a given disease in young subjects. When symptoms of thrombo-angitis obliterans first appear in the fourth decade, the maximum life expectancy is about twenty years, with somewhat more than one half the patients surviving for ten years or more.

CAUSE OF DEATH

In table 1 the causes of death have been classified under four headings: (1) operative intervention, (2) intercurrent disease, (3) asthenia and cachexia, and (4) vascular accidents. In the last group are included five instances of sudden death.

1 *Operative Intervention*—Seven patients died after operations which were necessary because of extensive vascular occlusions in the extremities or succumbed after surgical procedures (ganglionectomy) undertaken to stay the progress of the disease. The most common operation performed for thrombo-angitis obliterans is amputation. A high mortality is not usually associated with this procedure. In some cases a fatal issue can be explained by the fact that amputation is undertaken too late. Under such circumstances, the patient, worn out by sleepless nights of persistent pain and weakened by toxic absorption from a gangrenous extremity, readily succumbs to this relatively mild procedure. In the present-day conservatism lies some danger in occasionally delaying too long the surgical removal of a hopelessly diseased part. In the majority of cases natural demarcation and spontaneous amputation occur, but in some instances rising temperature, rapid pulse or a spreading gangrenous or infective process with a constitutional reaction demand early amputation to save life. Amputation in the presence of infection is particularly hazardous, as infection of the stump is likely to occur, to be followed by general sepsis or death. One case exemplifies this point (case 1). Postoperative accidents, such as pulmonary embolism, cardiac failure and hemorrhage, are other modes of termination (cases 6 and 2). Ganglionectomy in one of the six cases was performed in another

¹⁰ These cases represent the course of the disease before newer methods of treatment were instituted. Our more recent experience leads us to believe that the prognosis as to duration of life can be considerably extended.

hospital and was followed by a fatal intra-abdominal hemorrhage (case 5) The reduction of postoperative death lies within easy reach Early diagnosis, energetic treatment, careful follow-up and control of the cases long after the symptoms of diminished circulation have disappeared decrease the necessity for amputation

2 Intercurrent Disease, Accident and Suicide—In this group of twelve patients, ten died of nonvascular disease, one of suicide and one of accident Malignant neoplasms accounted for five of the ten fatalities, the other causes being appendicitis erysipelas and pulmonary infections No special organic involvement or a particular type of neoplasm can be associated with thrombo-angitis obliterans With longer survival an increased incidence of such intercurrent disease can be predicted

One suicide occurred in this group (case 16) Thrombo-angitis obliterans is a chronic disease enduring for many years Until the patients come under treatment there is often constant pain, with sleepless nights and forced retirement from economic usefulness It is not altogether strange that psychic morbidity arising from such a life prompts a few to end their suffering

The last patient of these nine, a window cleaner, fell to death from a height (case 15) This particular occupation has an acknowledged hazard But, as will be shown later, persons with thrombo-angitis obliterans frequently suffer vascular occlusions in various parts of the body Perhaps a thrombosis of a coronary or cerebral artery precipitated the fall Unfortunately, the autopsy was incomplete in this case

3 Asthenia and Cachexia—Six cases fall into this division Two patients had been operated on, but the stumps did not heal (cases 20 and 21) During the long period of hospitalization, progressive gangrene of the stump, for which further surgical intervention was impossible, resulted in death In the other four patients severe pain, stubborn ulcerations and gangrene of the fingers with infection caused progressive deterioration and death (cases 22, 23, 24 and 25) Addiction to morphine acquired during this period was an additional factor Unless the diagnosis is made early the arterial closures become so extensive that the ulcerations grow in size, the gangrene spreads and the operative wounds do not heal Infection finds little resistance in impoverished tissues, and death ensues from toxemia Although therapy has become more effective in the past decade there still occur instances of thrombo-angitis obliterans which first come under observation in an advanced stage Such cases, in spite of all therapeutic procedures in cooperative patients make steady unfavorable progress Until more effective remedies are discovered these cases must be expected occasionally

4 *Vascular Accidents and Sudden Death*—Twenty-two of the forty-seven cases discussed here belong in this category. A clinical diagnosis of coronary thrombosis was given in thirteen (cases 31, 32, 34, 35, 36, 38, 39, 40, 41, 42, 43, 46 and 47), three patients had intra-abdominal thromboses (cases 33, 44 and 45), and one died after a cerebrovascular closure (case 37). The details of the clinical pictures and the basis for the diagnoses for some of these cases will be found in the clinical résumés and in the postmortem observations.

Five cases of sudden death were also included in this group (cases 26, 27, 28, 29 and 30). Sudden death most often occurs in persons with heart disease (Reuter¹¹ and Vibert¹²). In apparently healthy persons coronary vascular accidents account for the vast majority of sudden deaths (East and Bain¹³ and White¹⁴). The probable mechanism of these deaths is the onset of ventricular fibrillation which so often follows acute obstruction of the coronary arteries (Fulton¹⁵ and Smith¹⁶). Cerebrovascular accidents usually cause a much slower death. In a discussion of the cause of sudden death in patients suffering from peripheral vascular thromboses, an embolic cause of sudden death must be considered. Pulmonary emboli must be extremely large to be quickly fatal. When repeated embolization of the lungs occurs, death may ensue suddenly after a number of the branches of the pulmonary artery have been plugged. In such cases there is a clear history of the earlier embolic episodes, as in case 6. In the latter instance the origin of the emboli was a mural thrombus in the ventricle on the right side following an occlusion of the coronary arteries and myocardial infarction. Cerebral emboli from thrombi in the extremities can occur only in the presence of a congenital cardiac defect. Otherwise, in the absence of endocarditis, mural thrombi of the left ventricle situated over myocardial infarcts would have to be postulated to explain such emboli. With all these points clearly in mind, we believe that it is a safe assumption that the five sudden deaths resulted from vascular accidents in the coronary vascular system or possibly in the cerebral arteries. Unfortunately, autopsies were not obtained in any of the five cases.

Disease and Thrombosis of the Coronary Arteries. A diagnosis during life of disease or thrombosis of the coronary arteries was made

11 Reuter, F. *Wien klin Wchnschr* **39** 1086, 1926.

12 Vibert, C. *Ann d'hyg pub et de med leg* **33** 193, 1895.

13 East, C. F. T., and Bain, V. W. C. *Recent Advances in Cardiology*, Philadelphia, P. Blakiston's Son & Co., 1929.

14 White, P. D. *Heart Disease*, New York, The Macmillan Company, 1930.

15 Fulton, F. T. *Am Heart J* **1** 138, 1925.

16 Smith, F. M. *Ligation of Coronary Arteries*, *Arch Int Med* **22** 8 (July) 1918.

in thirteen cases (31, 32, 34, 35, 36, 38, 39, 40, 41, 42, 43, 46 and 47), or the patients died of what was considered a sudden coronary occlusion. Autopsies were obtained in only five cases (31, 42, 43, 46 and 47). Case 43 has already been reported by Buerger¹⁷. In this patient a thrombotic occlusion of the left anterior descending coronary artery was found, the microscopic examination established the presence of arteriosclerosis. It must be noted that this patient died at the age of 24, a rather unusual age for arteriosclerotic disease and thrombosis of the coronary arteries. Occurring with thrombo-angitis obliterans, it takes on added significance, raising the question of the association of the two conditions. This will be discussed later. In the second patient (case 31) arteriosclerosis of the coronary arteries was present without thrombosis. The third case (42) showed myocardial infarction, both old and recent, with calcification of the left anterior descending artery, occlusion of the left circumflex artery and arteriosclerosis of the right coronary artery. A thrombotic occlusion (old and fresh) of the left anterior descending coronary artery with myocardial infarction was revealed in case 46, and occlusion of the left anterior descending coronary artery and an old occlusion of a large branch of the right coronary artery in case 47. Notwithstanding the absence of postmortem studies in the other eight cases the diagnosis was reasonably certain. In the past fifteen years the picture of disease and thrombosis of the coronary arteries has become clinically recognizable with ease and certainty. If the five cases of sudden death are added to the thirteen here, this group represents 38.5 per cent of all the fatal cases.

Other observers have commented on the occurrence of involvements of the coronary arteries in cases of thrombo-angitis obliterans. Lemann,¹⁸ reviewing the literature until 1928, found three cases which had come to autopsy and added one. Jager,¹⁹ in a recent comprehensive article concerned with the pathologic process of thrombo-angitis obliterans, described two patients who were found to have thrombosis of the coronary arteries at autopsy. He cited an additional case reported by Durck, of a man of 40, who died with the manifestations of heart disease. At postmortem examination the coronary arteries were extremely narrowed. The lesions considered specific by Buerger were not seen. Allen and Willius²⁰ reported seven instances, clinically diagnosed, of disease of the coronary arteries in a series of two hundred and twenty-five living patients with thrombo-angitis obliterans at the Mayo Clinic.

17 Buerger, L. *The Circulatory Disturbances of the Extremities*, Philadelphia, W. B. Saunders Company, 1924.

18 Lemann, I. I. *Am J M Sc* **176** 807, 1928.

19 Jager, Ernst. *Virchows Arch f path Anat* **284** 526, 1932.

20 Allen, E. V., and Willius, F. A. *Ann Int Med* **3** 35, 1929.

They concluded that "incidence of disease of the coronary arteries in thrombo-angitis obliterans as it occurs in our experience is probably not materially greater than the association with other diseases in the same age group" Samuels and Feinberg²¹ examined fifty patients by all available methods for evidence of disease of the coronary arteries and found that "five of these cases (10 per cent) showed definite clinical or electrocardiographic evidence of myocardial damage, presumably due to coronary artery lesions" Barron and Linenthal,²² directing attention to the general distribution of the disease in the body, suggested that disease of the coronary artery in the younger age groups, in the absence of peripheral vascular disease, might well be due to thrombo-angitis obliterans of these vessels As yet there is no clear evidence for this view, with which we find it difficult to agree

Although from a study of our cases no definite stand can be taken about the incidence of disease of the coronary arteries in living patients with thrombo-angitis obliterans, it is strikingly evident that a relatively large number of patients (38.3 per cent) died as a result of what can be suspected clinically to be disease of the coronary arteries We are not acquainted with any reliable statistics giving the incidence of death from coronary thrombosis in the general population in the age groups represented by our patients, but it is our impression that it is much less than 38 per cent It is true that the typical lesions of thrombo-angitis obliterans have never been definitely identified in the coronary vessels Nevertheless the greater incidence of sclerosis and thromboses in the coronary arteries of patients with thrombo-angitis obliterans is a significant occurrence, suggesting that there is more than a casual association between these two conditions

Cerebral Thrombosis One patient (case 37) died at the age of 44, after an attack of hemiplegia He had had thrombo-angitis obliterans for five years, during which time one leg had been amputated No autopsy was permitted, so the vessels could not be examined The occurrence of cerebral manifestations in thrombo-angitis obliterans has been recorded in the literature Buerger¹⁷ described one patient (our case 43) who died manifesting cerebral symptoms, to which Buerger drew special attention Autopsy on two of our patients (cases 46 and 47), who died of occlusion of the coronary arteries, revealed some cerebral vascular closures also Barron and Linenthal²² described two cases of clinical thrombo-angitis obliterans in which hemiplegia

21 Samuels, S., and Feinberg, S. *Am Heart J* 6:255, 1930

22 Barron, M. E., and Linenthal, H. *Thrombo-Angitis Obliterans*, *Arch Surg* 19:735 (Oct) 1929

appeared in the absence of hypertension or syphilis. In addition they cited Cserna's²³ case in which there was cerebral involvement. Oppel²⁴ published an instance of thrombo-angitis obliterans with thrombosis of the vertebral artery and hemiplegia (quoted by Barron and Linenthal). In a recent paper Bauer and Recht²⁵ described a patient who had suffered repeated cerebrovascular occlusions, and they quoted an additional case reported by Friedmann. In this last case histologic examination of the cerebral vessels seemed to confirm the diagnosis of thrombo-angitis obliterans. Two of Jager's¹⁹ patients had cerebral symptoms, and after death examination revealed multiple cerebral vascular closures. In the experience of one of us (S. S.) cerebral involvement clinically has been observed in many patients. There has been no opportunity to obtain pathologic confirmation in any of these cases. In the absence of syphilis, hypertension, intracranial tumors, hemorrhagic disease or multiple sclerosis, intracerebral vascular occlusion in relatively young persons who have occlusive peripheral vascular disease is of considerable significance. In addition to emphasizing the frequency of thrombotic processes (whatever their underlying pathologic process) in thrombo-angitis obliterans, such occurrences raise the question of their relationship to the underlying disease.

Intra-Abdominal Thromboses. Three cases (33, 44 and 45) are listed under this heading. Two of these have been reported by Bueiger¹⁷. The remaining case (33) is of interest because of the nature of the microscopic lesions in the thrombosed celiac and mesenteric arteries. This will be discussed later.

Aside from the two cases reported by Bueiger (our cases 44 and 45), we have found only a few other reports of cases of intra-abdominal vascular occlusion in patients with thrombo-angitis obliterans. Meyer²⁶ reported the case of a man who had thrombo-angitis obliterans from the age of 31. Both legs were amputated, the first one at 35 and the other at 37. At the age of 47 an illness characterized by distention, abdominal cramps, vomiting and visible peristalsis suggested the diagnosis of occlusion of the mesenteric artery, which was confirmed at operation. Among the cases discussed by Jager¹⁹ which came to autopsy, five showed thrombotic occlusion of intra-abdominal vessels: the superior and inferior mesenteric, renal, spermatic and suprarenal arteries and the abdominal aorta. Our third case (33) is an addition to the record.

²³ Cserna, S. *Wien Arch f inn Med* **12** 213, 1926.

²⁴ Oppel, V. A., quoted by Barron and Linenthal²⁴.

²⁵ Bauer, J., and Recht, G. *Wien Arch f inn Med* **23** 11, 1932.

²⁶ Meyer, J. Intermittent Claudication (Thrombo-Angitis Obliterans) Involving the Intestinal Tract, *J A M A* **83** 1414 (Nov 1) 1924.

Mesenteric thrombosis with Ortner's syndrome was suspected in two other cases (23 and 30), but because of the nature of the deaths they were included in other groups. In case 23 autopsy confirmed this clinical impression. It is well to keep in mind that colicky pains, spasmodic abdominal discomfort, intractable intestinal gaseousness, diarrhea or bloody stools in a person with peripheral vascular disease may indicate mesenteric arterial thrombosis. Here again the association between visceral thromboses and thrombo-angitis obliterans is so striking that it is difficult to accept an accidental relationship.

COMMENT ON CASES IN GROUP 4

This group is comprised of patients with thrombo-angitis obliterans who succumbed to vascular accidents in parts of the body apart from the extremities. These observations assume greater interest when it is recognized that this group of patients represents almost 50 per cent of all the cases presented here (twenty-two of forty-seven). If the twelve patients who died of intercurrent nonvascular disease, accident or suicide are omitted, this group represents 63 per cent of the total (twenty-two of thirty-five).

Of interest and importance is the nature of the occlusive vascular process occurring in the heart,²⁷ brain or intestinal and other intra-abdominal vessels.

It is difficult to believe that thrombo-angitis obliterans is restricted solely to the vessels of the extremities. Jager,¹⁹ who studied the problem intensively, seemed convinced that the pathologic changes which he considered characteristic of the disease are the same for the different sizes of arteries in all parts of the body, and he concluded that thrombo-angitis obliterans occurs in the most widespread and different sites. Those particularly interested in the pathologic process of thrombo-angitis obliterans are referred to the thorough and illuminating contributions of Jager. Others have suggested the likelihood of involvement of other parts (Barton and Linenthal,²² Lemann,¹⁸ Bueiger¹⁷). None of the last-mentioned workers could confirm their impressions with pathologic evidence. However, when in a series of forty-seven patients it can be demonstrated that twenty-two succumbed to visceral vascular

²⁷ Perla in a recent letter to one of us (S. H. A.), in which he commented on his case of thrombo-angitis obliterans of the coronary arteries, said in part: "The case was a bona fide instance of thrombo-angitis obliterans. The coronary arteries were severely involved in apparently a mixed process. There was arteriosclerosis of the coronary vessels with a recent thrombotic occlusion. In view of the fact that the lower portion of the aorta and iliac arteries showed evidence of thrombo-angitis obliterans, it was considered that the thrombosis of the coronary arteries was part of the same process. I could not find, however, evidence of acute inflammation of the coronary arteries."

accidents, it becomes evident that an inconsistency exists. The solution probably lies in the pathologic criteria. Only in the acute stages of the disease, when all the arterial layers are involved in an inflammatory process, infiltrated with polymorphonuclear leukocytes, with purulent foci and giant cells in the lumen and red thrombus masses occluding the vessels, can the pathologic diagnosis of thrombo-angitis obliterans be made with certainty. Buerger stated that such lesions are uncommon in the deep vessels of the extremities. Perla²⁸ did not see one such lesion in any of the extremities he examined. One of us (S S), in the examination of a large number of amputated extremities, did not find these typical lesions in the deep vessels. How unlikely it is, then, that one should find such lesions in the inaccessible and relatively less frequently involved internal organs. Concerning the pathologic picture in the later end stages, the differentiation between thrombo-angitis obliterans and arteriosclerosis in the vessels of the extremities can be made. The involvement of veins and nerves and the relatively spared internal elastic layer in the artery serve to denote the thrombo-angitic process. In the other organs of the body, however, the end-stage of many types of occlusive vascular disease with thromboses presents the same pathologic picture. Special features which might be of aid in defining the origin of the process cannot be identified. The problem of correctly interpreting these pathologic pictures is made more difficult by reason of the fact that arteries involved in any process become the site of marked secondary arteriosclerotic changes which often overshadow and obscure the characteristic lesions of other diseases. The general inaccessibility of these internal organs, the infrequent opportunity one has to examine such organs early in the disease, the paucity of postmortem material and, until recently, the lack of attention to the problem are all factors which have retarded a satisfactory solution of the difficulty.

It is not the purpose of this article to discuss the detailed pathologic aspects of this problem. We merely wish to point out that as pathologic studies fail to establish the diagnosis of thrombo-angitis obliterans in the vessels of the thoracic or abdominal organs, the acceptance of the occurrence of the disease in these organs for the time being must be presumptive. Therefore, great significance must be attached to the fact that a considerable percentage of patients with thrombo-angitis obliterans die of vascular accidents. If these visceral vascular processes are not identical in nature with that in the peripheral vessels, it may be that the presence of thrombo-angitis obliterans in a person predisposes him

²⁸ Perla, D. Surg., Gynec. & Obst. **41** 21, 1925

to abnormal thrombotic tendencies or to early degenerative general vascular changes, or that these patients possess a constitutional inferiority of the entire vascular system which displays local variations. We wish to emphasize that we cannot establish from the pathologic data available the nature of the extrapedal vascular processes, nor do we wish to record a dogmatic opinion. It is our purpose to point out that such vascular thromboses and occlusions occur in many vessels of the body in cases of thrombo-angitis obliterans. Until the pathologic process of vascular disease in general receives more detailed description and classification the diagnosis of thrombo-angitis obliterans in the visceral vessels will be a clinical achievement more often than a pathologic one.

OBSERVATIONS AT AUTOPSY

Published reports of pathologic data on cases of thrombo-angitis obliterans coming to autopsy are rare. We found only those of Buerger (three cases), Peila (one), Lemann (one), Dean Lewis²⁹ (one) and Jager (seven).

Nineteen of our cases, which include the three described by Buerger, came to autopsy. Summaries of the relevant observations are appended to the clinical abstracts.

In eleven (58 per cent) of the nineteen vascular thromboses occurred in arteries other than those of the extremities. They were situated variously in the hepatic artery (case 31), coronary arteries (cases 6, 33, 42, 43, 46 and 47), celiac axis (cases 33 and 45), mesenteric vessels (cases 23, 33, and 45), abdominal aorta (cases 6, 20 and 44) and cerebral vessels (cases 46 and 47). The last case (15) cannot be classified as examination was incomplete. No attempt will be made here to discuss the more detailed microscopic pathologic changes in the visceral and coronary vessels which were thrombotically occluded. In all the arteries examined in all the cases except one (33) the lesions of arteriosclerosis were readily identified. The inclusive nature of such a pathologic picture has already been commented on. In case 33 there was thrombosis of the celiac axis, the superior and inferior mesenteric arteries and the right coronary artery. The lesions in the celiac axis, particularly, suggested thrombo-angitis obliterans. An organized thrombus with occlusion and recanalization, minimal changes in the internal elastic layer and the presence of cells containing iron pigment were the features which warranted the opinion that the usual type of arteriosclerotic change did not exist here. Similar microscopic pictures were seen in

²⁹ Lewis, Dean. Spontaneous Gangrene of the Extremities, Arch Surg **15** 613 (Oct) 1927.

sections of the superior and inferior mesenteric arteries. These resembled those described by Buerger as the "old type" of lesion in the extremities.

Examination of the autopsy material revealed the presence of the accepted arterial lesions considered pathognomonic of thrombo-angitis obliterans in the extremities in only one (case 33) of the nineteen cases examined. Nevertheless, the fact already emphasized, that thromboses occur in parts of the body other than the extremities in cases of thrombo-angitis obliterans was amply confirmed.

Lewis Conner³⁰ recently pointed out that arterial thromboses in the abdominal viscera are probably more common than is generally appreciated. He suggested application of our knowledge of the events following a thrombosis of the coronary or cerebral arteries to the problem of the recognition of visceral vascular occlusion. This admonition to consider the possibility of visceral arterial thromboses applies particularly to patients with thrombo-angitis obliterans, for, as has been shown, such thromboses are common and not infrequently are the cause of the fatal termination in this disease.

SUMMARY

1 The clinical and pathologic data of forty-seven patients who died of thrombo-angitis obliterans are presented.

2 The extremities involved, the number of amputations, the age of incidence and the duration of the disease are discussed.

3 The causes of death are classified in 4 groups: (1) operative intervention (7 cases), (2) intercurrent disease, accidents and suicide (12 cases), (3) asthenia and cachexia (6 cases), and (4) extraperipheral occlusive vascular accidents and sudden death (22 cases). Each of these groups is discussed.

4 Particular attention is directed to the predominance of vascular occlusions in parts of the body other than the extremities. Cases with coronary thrombosis, mesenteric or cerebral arterial thromboses are grouped and discussed. It is suggested that the occurrence of these phenomena in cases of thrombo-angitis obliterans is not merely coincidental and that there exists some significant connection between the multiple visceral and cerebrovascular thromboses and the clinically typical involvement of the vessels in the extremities.

5 The pathologic aspect of the problem of the existence of thrombo-angitis obliterans in vessels other than those in the extremities is briefly commented on.

³⁰ Conner, Lewis A. *Am J M Sc* **185** 13, 1933

6 Nineteen cases brought to autopsy are considered. Analysis confirms the frequent occurrence of visceral and cardiac arterial thromboses in thrombo-angiitis obliterans.

CONCLUSION

A consideration of the causes of death of forty-seven patients who had thrombo-angiitis obliterans reveals that such patients often die as a result of thromboses in the arteries of the heart, brain and intestines. The frequency of such vascular involvement forces the conclusion that a bona fide association doubtless exists and that the thrombotic occlusive manifestations outside the extremities are related to the established disease process.

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INFECTION AND THE TOLERANCE FOR DEXTROSE

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Diseases of a cutaneous nature have long been associated with the ingestion of carbohydrate. The introduction of modern biochemical and micro-analytic methods has made possible the investigation of this interesting relationship. In addition the field has been enlarged, and now includes a variety of infections other than those essentially dermatologic. The problem, however, as a scientific study is complicated by the many factors involved in carbohydrate metabolism, each of which takes part in the transformations which the carbohydrate molecule undergoes in the animal body.

The first studies in this field were devoted primarily to an examination of the values for blood sugar after fasting in the more common dermatoses: acne vulgaris, seborrhea, psoriasis, sycosis, eczema, dermatitis rosacea, urticaria, etc. Earlier investigators (Schwartz, Highman and Malinkin,¹ Levin and Kahn,² McGlasson,³ Haldin-Davis and Wills⁴) reported hyperglycemia with fasting in most of the aforementioned conditions. The more recent studies, however, have not confirmed the earlier work. Thus, in 462 dermatologic cases Loeb⁵ noted hyperglycemia only in dermatitis intertriginosa. Muller,⁶ Stricker and his co-workers⁷ and Matsumoto⁸ also found no pathologic increase in blood sugar if glycosuria was absent. Concerning their 875 dermato-

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1 Schwartz, H J, Highman, W J, and Malinkin, H C. *J Cutan Dis* **34** 159, 1916.

2 Levin, D L, and Kahn, M. *Am J M Sc* **164** 379, 1922.

3 McGlasson, I L. Hyperglycemia as an Etiologic Factor in Certain Dermatoses, *Arch Dermat & Syph* **8** 665 (Nov) 1923.

4 Haldin-Davis, H, and Wills, L. *Brit J Dermat* **37** 364, 1925.

5 Loeb, H. *Arch f Dermat u Syph* **152** 113, 1926.

6 Muller, A. *Arch f Dermat u Syph* **157** 639, 1929.

7 Stricker, A, and Saylor, M A. Sugar Metabolism in Acne Vulgaris, *Arch Dermat & Syph* **20** 705 (Nov) 1929. Stricker, A, and Adams, P D. Blood Sugar Metabolism in Certain Dermatoses, *ibid* **26** 1 (July) 1932.

8 Matsumoto, Y. *Jap J Dermat & Urol* **30** 107, 1930.

logic cases Schamberg and Brown⁹ stated that "we have been impressed with the comparatively small part which hyperglycemia plays in the production of cutaneous diseases" In a recent study of 600 patients with the more common diseases of the skin Fisher¹⁰ reported that hyperglycemia was rarely found, and that the determination of the blood sugar possessed no diagnostic value Tauber¹¹ (511 cases) also reported no hyperglycemia in common disorders of the skin In fact, in a series of 189 cases of furunculosis he administered dextrose intravenously for six successive days, and stated that the results were remarkably good From this brief résumé it seems obvious that the value for blood sugar obtained after fasting in dermatologic conditions possesses no diagnostic value, since significant variations from normal apparently rarely occur

The tolerance for dextrose has been studied in connection with cutaneous disorders with results somewhat more conflicting Mannino¹² utilized the test in 52 dermatologic cases, and observed no appreciable alteration in carbohydrate metabolism In a similar study Greenbaum¹³ reported "If there is any connection between the intake of sugar and pustular acne or if intolerance for sugar is part of an endocrine imbalance generally believed to be present in acne, this test does not appear to be of help in detecting it" In 1932 Rost,¹⁴ utilizing a technic for the injection of dextrose intravenously for the tolerance test, found no pathoglycemic curves in the common cutaneous disorders On the other hand Ayres¹⁵ found that the values for blood sugar at various periods of the dextrose tolerance test were higher than the average values at corresponding periods in clinically normal people Confirmatory evidence has been presented by Usher,¹⁶ Norducci,¹⁷ Fugino¹⁸ and Campbell¹⁹ Somerford²⁰ recently studied the blood sugar at forty-five and

9 Schamberg, J F., and Brown, H Chemistry of the Blood in Diseases of the Skin, Arch Dermat & Syph **21** 1 (Jan) 1930

10 Fisher, J E Blood Sugar Findings in the More Common Diseases of the Skin, Arch Dermat & Syph **26** 970 (Dec) 1932

11 Tauber, E B Hyperglycemia in Diseases of the Skin, Arch Dermat & Syph **27** 198 (Feb) 1933

12 Mannino, L Gior ital di dermat e sif **69** 1603, 1928

13 Greenbaum, S S Tolerance for Glucose in Acne Vulgaris, Arch Dermat & Syph **23** 1064 (June) 1931

14 Rost, G A Brit J Dermat **44** 57, 1932

15 Ayres, S Jr Glucose Tolerance Reactions in Eczema, Arch Dermat & Syph **11** 623 (May) 1925

16 Usher, B Relation of Carbohydrate Metabolism to Eczema, Arch Dermat & Syph **18** 423 (Sept) 1928

17 Norducci, F Gior ital di dermat e sif **70** 857, 1929

18 Fugino, S Acta dermat **16** 567, 1930

19 Campbell, G G Brit J Dermat **43** 297, 1931

20 Somerford, A R Brit J Dermat **44** 476, 1932, Lancet **2** 1140, 1929

ninety minute intervals after the oral ingestion of 50 Gm of dextrose. He concluded that

In cases of eczema an increased amount of sugar in the blood occurred in those types in which there was an exudation present in the epidermis, either intracellular or extracellular, but as soon as the exudation was allowed to escape externally (in which case it could be assumed that it was being absorbed into the blood stream in smaller amounts than before) there was a decrease in the blood-sugar content. It seems probable from this finding, therefore, that the hyperglycemia is due to the absorption of epidermal products present in the cutaneous exudate.

It seems apparent, therefore, that the majority of investigators feel that a disturbance in the carbohydrate mechanism is present, as shown in most dermatologic diseases by the dextrose tolerance test.

In regard to acute febrile conditions, Sick²¹ reported normal blood sugar after fasting but the blood sugar curve was still abnormally high four hours after the ingestion of dextrose. However, Andresen and Schmidt²² studied cases of malaria, typhoid fever, measles, erysipelas, scarlet fever and dysentery during the febrile period and found, with the exception of measles, higher rather than normal values for the blood sugar after fasting. Geiger²³ and Weiland²⁴ noticed the development of hyperglycemia with fasting during the period of rising temperature in febrile conditions with a subsequent return to normal as the temperature fell. Williams and Dick²⁵ found glycosuria present in 41 per cent of their patients with acute infectious diseases (scarlet fever, diphtheria, pneumonia, influenza). This glycosuria was accompanied by a lowered carbohydrate tolerance, as shown by dextrose tolerance curves both in acute infectious conditions and in experimental infections produced in animals. They found that the administration of insulin improves the animal's tolerance for dextrose and suggested that in infectious and febrile diseases there is often an injury to the islets of Langerhans with a consequent lowered production of insulin. Labbe and Boulin²⁶ observed glycosuria and disturbed carbohydrate tolerance in most of their febrile patients. Sweeney and Lackey²⁷ performed daily dextrose tolerance tests on rabbits in which toxemias had been produced with diphtheria toxin. Under these experimental conditions toxic rabbits

21 Sick, W. *Munchen med Wchnschr* **78** 609, 1931.

22 Andresen, J., and Schmidt, S. *Klin Wchnschr* **6** 213, 1927.

23 Geiger, E. *Klin Wchnschr* **4** 1265, 1925.

24 Weiland, H. *Munchen med Wchnschr* **60** 706, 1913.

25 Williams, J. L., and Dick, G. F. Decreased Dextrose Tolerance in Acute Infectious Diseases, *Arch Int Med* **50** 801 (Dec) 1932.

26 Labbe, M., and Boulin, R. *Bull et mem Soc med d hop de Paris* **3** 1358, 1925.

27 Sweeney, J. S., and Lackey, R. W. Effect of Toxemia on Tolerance for Dextrose, *Arch Int Med* **41** 257 (Feb) 1928.

revealed a distinct decrease in tolerance for dextrose which became more marked as the toxemia progressed. They felt this to be suggestive of a quantitative relationship between toxemia and tolerance (or rather intolerance) for dextrose. In a second series of rabbits ill from diphtheria toxin 2 units of insulin was injected daily, fifteen minutes after the administration of dextrose. The toxemia appeared to have little if any effect on the injected insulin. On the basis of these experiments Sweeney²⁸ suggested that the effect of toxemia is to suppress the endogenous production of insulin. Downie²⁹ and his associates and Schwentker and Noll³⁰ reported similar findings. On the other hand Lawrence and Buckley³¹ found that the action of insulin is inhibited by diphtheria toxin in rabbits, and at necropsy noted signs of overactivity in the thyroid and suprarenal glands.

Along somewhat similar lines Delafield³² recently studied the effect on rabbits of suspensions of dead organisms injected intravenously. He found that gram-positive organisms produced no obvious illness and no significant changes in the blood sugar or in the blood inorganic phosphorus. However, eight of twelve gram-negative organisms produced illness with hyperglycemia and low inorganic phosphorus. Delafield concluded that it could not be asserted that the hyperglycemic substance is identical in the different bacteria tested, but that such a substance exists was suggested by the work of Menten and King,³³ who found that the precipitate obtained from a filtrate of a culture of *Bacillus aertrycke* produced a rise in blood sugar and toxic effects. When pus from metastatic abscesses or blood serum taken from persons with diabetes mellitus complicated by infection is mixed with insulin, its ability to lower the blood sugar is decreased.³⁴ Buckley³⁵ noted that the subcutaneous injection of trypsin tends to inhibit the action of insulin in rabbits.

Kohn and Felshin³⁶ found that in children with lobar pneumonia a dextrose tolerance test within two days after the crisis gave a diabetic-like blood sugar curve. When the test was performed more than two

28 Sweeney, J. S. Effect of Toxemia on Tolerance for Dextrose and on the Action of Insulin, *Arch Int Med* **41** 420 (March) 1928.

29 Downie, E. M. *J Australia* **1** 813, 1930. Long, M., and Downie, E. **1** 647, 1932.

30 Schwentker, F. F., and Noll, W. W. *Bull Johns Hopkins Hosp* **46** 259, 1930.

31 Lawrence, R. D., and Buckley, O. B. *Brit J Exper Path* **8** 58, 1927.

32 Delafield, M. E. *J Path & Bact* **35** 53, 1932.

33 Menten, M. L., and King, C. G. *J Infect Dis* **46** 275, 1930.

34 Depisch, F., and Hasenori, R. *Ztschr f d ges exper Med* **58** 110, 1927.

35 Buckley, O. B. *Brit J Exper Path* **12** 13, 1931.

36 Kohn, J. L., and Felshin, G. Dextrose Tolerance Tests Following Lobar Pneumonia in Children, *Am J Dis Child* **39** 512 (March) 1930.

days after the crisis the blood sugar curve was normal. Acetone was present during the febrile period. But, according to Binger, Hastings, Sendroy, Malt and Morgan,³⁷ true ketosis does not exist during lobar pneumonia. Recently Geoffrey, Mitchell and Kolb³⁸ observed an interesting relationship between the acid-base balance of the blood and tolerance for dextrose. They found that the ingestion of large amounts of ammonium chloride by young healthy male adults reduced the alkaline reserve of the plasma to a diabetic level—32 per cent by volume. When dextrose was given at this stage a definite intolerance was exhibited, shown by abnormally high blood sugar curves with a tardy return to normal but no glycosuria. Sodium bicarbonate produced little variation in the acid-base equilibrium or in the blood sugar response to the ingestion of dextrose. Mitchell and Kolb pointed out that the acidosis of diabetes may have a contributory effect on the changes in carbohydrate metabolism as encountered in this disease.

In a field less extensively studied, namely, the influence of pyogenic organisms on the carbohydrate metabolism, Picard³⁹ observed hyperglycemia after fasting, but no glycosuria, in patients with multiple carbuncles, furuncles or abscesses of various types. Nissle,⁴⁰ however, found that the blood sugar values of patients with staphylococcic and streptococcic infections with extensive inflammation (carbuncles, furuncles, abscesses, erysipelas) were always normal. Seitz⁴¹ studied sixteen streptococcic and forty staphylococcic infections, eighteen of the latter being due to carbuncles, besides several perinephritic abscesses. In no case was alimentary hyperglycemia present. On the administration of dextrose, however, the patients with carbuncles and perinephritic abscesses and, to a lesser degree, the remaining patients with staphylococcic infections showed a definite intolerance. On the other hand the cases of streptococcic infection revealed no impairment of carbohydrate metabolism—the blood sugar remaining within normal limits after the ingestion of dextrose.

Recently Evans, Riding and Glynn⁴² observed that oral sepsis in nondiabetic patients was usually associated with a slight but definite diminution in tolerance for carbohydrate, which improved on subsequent

37 Binger, Hastings, Sendroy, Malt and Morgan. *J Exper Med* **45** 1081, 1927.

38 Geoffrey, T., Mitchell, D. M., and Kolb, L. C. *Biochem J* **27** 1253, 1933.

39 Picard, H. *Deutsche med Wchnschr* **53** 1086, 1927.

40 Nissle, K. *Med Klin* **25** 1469, 1929.

41 Seitz, E. *Arch f klin Chir* **112** 809, 1919.

42 Evans, Riding and Glynn. *Brit Dent J* **48** 1116, 1927, *Lancet* **2** 592, 1927.

dental treatment Holcomb⁴³ previously reported 2 cases with similar results, in one of which there were infected teeth, and in the other sinusitis

Within the last generation the specific relationship between focal infection and arthritis has become well established in medical science Pemberton and his co-workers⁴⁴ discovered that "60 per cent of all arthritic patients present delay in the rate at which sugar leaves the blood after ingestion by mouth, and that this delay grows less or disappears after recovery from arthritis, whatever the treatment employed" Comparable results have been reported by Holsti,⁴⁵ Fletcher,⁴⁶ Warfield,⁴⁷ Hench⁴⁸ and Olmsted and Gay⁴⁹ That normal blood sugar curves are obtained on removal of the foci of infection or on recovery from arthritis has been confirmed by Pringle and Miller⁵⁰ Contradictory evidence has been obtained by Schackle and Copeman⁵¹ recently They stated "In several patients with true rheumatoid arthritis multiple curves were plotted at varying stages, the latter curves often being after several months' treatment with insulin (in most instances with great benefit clinically) but in no case was any remarkable improvement in the glucose tolerance curve observed Indeed, subsequent curves generally showed striking resemblances to those previously obtained"

It seems apparent, from this brief survey, that a general relationship exists between infection, whether dermatologic, febrile, inflammatory, dental or arthritic, and the carbohydrate tolerance test Whereas most workers report normal blood sugar values after fasting in these conditions, they almost uniformly agree that some abnormal factor concerning the carbohydrate mechanism is present in view of the fact that pathologic glycemic blood sugar curves are usually obtained on the ingestion of dextrose

The effect of cellulocutaneous infections on the rate of removal of sugar from the blood after the ingestion of dextrose has been studied but little Therefore the present work was devoted primarily to an investigation of the effect of pyogenic infections of cellular and connective tissues, generally included under the term cellulitis, on the dextrose

43 Holcomb, B J Lab & Clin Med **11** 874, 1925

44 Pemberton, R Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, 1929

45 Holsti, O Acta med Scandinav (supp) **3** 137, 1922

46 Fletcher, A A Dietetic Treatment of Chronic Arthritis and Its Relationship to the Sugar Tolerance, Arch Int Med **30** 106 (July) 1922

47 Warfield, L M J Michigan M Soc **22** 461, 1923

48 Hench, P S Atlantic M J **28** 425, 1925

49 Olmsted, W H, and Gay, L P Blood Sugar Curves Following a Standardized Glucose Meal, Arch Int Med **29** 384 (March) 1922

50 Pringle, G L K, and Miller, S Lancet **1** 171, 1923

51 Schackle, J W, and Copeman, W S C Brit M J **1** 268, 1933

tolerance test In addition a small group of systemic diseases with febrile manifestations and a considerable number of arthritic and rheumatoid conditions have been studied

PROCEDURE AND METHODS

The usual methods, technic and precautions were observed The quantity of dextrose used for a dextrose tolerance test varies both in this country and on the continent We used 15 Gm of pure dextrose per kilogram of body weight in about 300 cc of water to which ice and the juice of a lemon were added This fairly tasty drink was given in the morning after a twelve hour fast Nausea was rarely observed The patients were instructed to refrain from smoking during the course of the test This precaution was taken in view of the fact that Lundberg and Thysellus-Lundberg⁵² discovered that the blood sugar values rise on the consumption of tobacco, owing, they contend, to the fact that the nicotine stimulates the production of epinephrine

A specimen of blood (from 5 to 6 cc) was taken after fasting by venipuncture just prior to the ingestion of dextrose and transferred to a small jar containing 10 mg of dry, finely powdered sodium oxalate Similar samples of blood were taken at one hour, two hour and three hour intervals following the administration of the dextrose At the same time specimens of urine were collected Each specimen of blood was precipitated immediately by the Folin-Wu⁵³ method as modified by Haden⁵⁴ The blood sugar was determined by the Benedict⁵⁵ method and the blood urea by direct nesslerization⁵⁶ as modified by Looney⁵⁷ Every precaution was taken to insure accuracy of results Bacteriologic work was not performed in a number of cases because the patients entered the hospital with the infected area open and draining The data are given in tables 1, 2 and 3

RESULTS

Seventy-three cases have been studied during this investigation 36 presenting localized pyogenic infections, 9 generalized febrile conditions and 28 arthritis and rheumatism Eighteen of the cases of pyogenic infections, especially those with cellulitis, were studied in duplicate Thus a tolerance test was performed during the course of the infection, usually at the early acute stage when there was present, as a rule, a definite elevation of temperature and again when the condition had cleared up and the patient was ready to go home

Any discussion of glycemic curves necessitates observations on several points the fasting level, the height to which the blood sugar rises after the administration of the dextrose, the capacity of the tissues and

52 Lundberg, E, and Thysellus-Lundberg, S Acta med Scandinav (supp) 38 5, 1931

53 Folin, O, and Wu, H J Biol Chem 38 81, 1919

54 Haden, R L J Biol Chem 56 469, 1923

55 Benedict, S R J Biol Chem 68 759, 1926

56 Karr, W G J Lab & Clin Med 9 329, 1924 Schmidt, E G J Biol Chem 78 53, 1928

57 Looney, J M J Biol Chem 88 189, 1930

the glycogenic organs to remove sugar from the blood, or the speed with which the blood returns to the fasting level, and glycosuria. We have interpreted our data on the basis of a normal range of blood sugar levels after fasting of from 80 to 120 mg per hundred cubic centimeters of blood. In addition the blood sugar level should not rise above from 150 to 180 mg and should be back to the normal level after fasting, or slightly below, within two hours after the ingestion of dextrose. There should be no glycosuria at any time.

The data in table 1 indicate that pyogenic infections markedly decrease the patient's tolerance for dextrose or at least decrease the rate at which sugar is removed from the blood stream. Among the 36 patients given dextrose tolerance tests when the infection was at the acute stage, 29 (72 per cent) yielded distinctly abnormal curves. Practically all the patients with cellulitis gave diabetic-like blood sugar curves. A few with abscesses or subsiding infection yielded normal curves. As a rule, however, the blood sugar rose well above 180 mg per hundred cubic centimeters, frequently as high as from 250 to 350 mg. In addition the excess sugar was removed slowly from the blood stream, even at the two hour period it usually ranged from 150 to 317 mg. Despite these high blood sugar values only 4 cases showed appreciable glycosuria, which, incidentally, disappeared when the test was repeated after the infection had subsided. The dextrose threshold, therefore, is generally high during the course of an infection.

When the patient was ready to go home, after the infection had subsided and healing was practically complete, a second dextrose tolerance test gave blood sugar curves almost invariably within normal limits with no concomitant glycosuria. In most cases the improvement in carbohydrate tolerance was marked, as can be seen from table 1.

The most pathoglycemic curves were obtained in the types of streptococcic and staphylococcic infections which are generally included in the term cellulitis. This was particularly true in cases showing large, inflamed, pustular areas with an accompanying rise in temperature. However, an elevated temperature per se does not necessarily result in abnormal blood sugar curves (cases 30, 34, 35 and 36), also high blood sugar curves were frequently obtained when the temperature was within normal limits (cases 5, 10, 16, 22, 24, 25, 26 and 27).

Seitz⁴¹ found that infections (pyogenic) produced by streptococcic organisms do not influence dextrose tolerance curves, although infections by staphylococcic organisms do. Although the number of our cases in which bacteriologic examination was made is insufficient to permit definite conclusions to be drawn as to the specific effect of each group of organisms, the data suggest that the greater disturbance in carbohydrate metabolism is produced by the streptococcic organisms. This

TABLE 1—*The Effect of Pyogenic Infection on the Tolerance for Dextrose*

Case	Age	Sex	Date	Urea Nitrogen, Mg	Temper ature, F	Dextrose Tolerance Test					Bacteriology	Diagnosis
						Average Blood Sugar, Mg per 100 Cc				Urine Sugar		
						Fasting	1 Hr	2 Hrs	3 Hrs			
1	21	F	2/10 4/4	6.8 11.5	100.0 98.6	100 101	215 142	215 135	129 160	Negative Negative	Staph albus	Puncture wound in index finger with subsequent infection, lymphangitis, lymphadenitis
2	30	M	12/3 1/4	12.0 10.4	100.1 98.5	119 118	225 167	228 112	180 87	4+ (1st hr) Negative		Cellulitis of arm following phenol burn abscess of wrist, infectious dermatitis
3	44	M	2/14 4/18	6.8 10.7	99.2 98.5	111 100	182 140	161 110	71 74	Negative Negative	S haemolyticus, Staph aureus	Abscess of right arm, cellulitis of right arm
4	40	M	3/28 4/22	19.6 13.8	101.4 98.6	116 91	364 154	303 136	182 95	Trace Negative	S haemolyticus, Staph aureus	Abscess of scalp cervical lymphadenitis, osteo myelitis of outer table of skull
5	45	M	10/15 10/28	9.4 11.1	98.6 98.5	133 90	187 167	200 125	154 81	Negative Negative	S haemolyticus, Staph aureus	Lacerated and infected scalp, occipitofrontal abscess
6	62	M	9/24 10/21	7.9 8.8	100.0 98.6	128 114	200 194	213 160	108	Trace Negative	S haemolyticus, blood culture neg	Cellulitis of left leg
7	36	F	1/7 3/1	11.8	102.0 98.6	98 100	176 160	190 110	182 98	Negative Negative	S haemolyticus	Cellulitis of right arm, acute axillary lymph adenitis
8	41	M	1/9 2/25	11.0 12.1	101.0 98.5	102 107	180 161	204 127	177 89	Negative Negative	S haemolyticus	Cellulitis of right leg
9	41	M	11/1 2/9	10.8 98.5	100.8 98.5	105 104	179 170	200 122	194 95	++ Negative	S haemolyticus, Staph aureus	Gangrene of abdominal wall following an operation, intestinal obstruction
10	28	M	4/5 5/3	11.2	98.6 98.6	111 102	201 184	213 121	133 75	Trace Negative		Ischiorectal abscess
11	46	M	4/7 4/29	101.0 98.4	101.0 98.4	100 88	198 198	191 80	109 75	Negative Negative		Cellulitis of right forearm
12	44	M	2/4 4/7	14.6	101.0 98.5	87 111	185 169	185 95	117 95	Negative Negative	Staph aureus	Sacral carbuncle
13	31	M	3/4 4/15	11.5	101.6 98.5	116 102	244 170	196 111	139 95	Negative Negative	Staph aureus	Infected scrotal hematoma, inguinal hernia
14	51	M	2/15 2/29	11.5 13.0	99.4 98.6	100 103	167 184	200 184	167 161	Negative Negative		Cellulitis of left arm and forearm Infection still present

15	22	M	12/ 2 12/29	12 3	102 5 98 4	118 111	200 160	133 98	83 101	Negative Negative	Cellulitis of face, abscess of right molar
16	47	M	12/14 1/13	7 0	98 6 98 6	105 102	204 177	180 101	131 110	++ Negative	Inguinal abscess, inguinal lymphadenitis
17	39	M	12/15 12/30	10 1 9 0	100 1 98 5	91 100	174 118	164 74	92	++ + Negative	Carbuncle on neck, cellulitis of neck
18	53	M		87 2	103 0	160	364	317	274	Negative	Cellulitis of neck, lobar pneumonia
19	76	F		68 0	100 4	100	208	210	190	Negative	Cellulitis of arms, legs, abdomen, septiceemia, toxic nephritis
20	50	M		19 0	99 0	105	211	202	152	Negative	Staph aureus
21	29	M		13 0	101 2	100	200	152	65	Negative	Staph aureus
22	40	M			98 6	111	174	190	177	Negative	Carbuncle, multiple furunculosis, syphilis
23	25	F		7 1	99 0	100	177	142	111	Negative	Furunculosis of back, intestinal obstruction
24	40	M			98 5	125	200	108	133	Negative	Furunculosis
25	25	M		7 0	98 4	100	211	176	111	Negative	Felon on bone, osteoperiostitis of finger
26	55	M		20 6	98 7	127	286	253	197	Negative	Carbuncles
27	71	M		17 7	100 2	98	142	217	204	Lost	Staph albus, bacillus of Vincent's angina
28	34	F		7 1	98 6	105	233	167	105	Negative	Agranulocytic angina syphilis, infected mouth
29	42	M		15 0	99 8	100	170	155	125	Negative	superficial infection of genitals
30	30	M		13 0	101 0	100	127	118	91	Negative	Syphilitic ulcers (tertiary), bronchitis, hypertensive cardiovascular disease
31	46	M		18 4	98 6	87	182	125	95	Negative	Tenosynovitis of shoulder, purulent otitis media
32	35	M		10 5	98 7	95	148	97	66	Negative	Salpingitis, syphilis
33	15	M		10 9	98 4	100	125	105	83	Negative	Subacute bacterial endocarditis, rheumatic cardiovascular disease, syphilis
34	15	M		13 3	101 0	91	120	100	90	Negative	Subsiding cellulitis of right foot
35	15	F		10 6	99 4	77	148	85	74	Negative	Furunculosis of left external ear
36	48	M		11 6	100 0	100	125	123	110	Negative	Staph aureus
											Staph aureus
											Staph aureus
											S viridans (sputum)
											Palmar abscess five days after surgical drainage
											Infected bursa of right knee
											Chronic abscess of breast; syphilis
											Pulmonary abscess, caries, pyorrhea

disturbance in carbohydrate tolerance seems to be even greater, however, when the infection is due to a mixture of these two groups of organisms. We hope to study this phase of the problem more extensively.

The data in table 1 can best be summarized by averaging all the blood sugar values for each test interval. This has been done for the tests performed both during and after the infection, with the results shown in table 2. From table 2 it can readily be seen that the average blood sugar curve during a pyogenic infection is higher and much more prolonged than that given by the normal person. In addition the average curve secured after the infection has subsided comes easily within normal limits. Hence the disturbance in carbohydrate metabolism produced by this type of infection is only temporary.

While many workers have reported high blood sugar values after fasting during infection, especially if the temperature is above normal,

TABLE 2—*Average Blood Sugar Values for Each Test Interval in Cases of Pyogenic Infections*

Time	During Infection		After Infection	
	Number of Determinations	Average Blood Sugar, Mg per 100 Cc	Number of Determinations	Average Blood Sugar, Mg per 100 Cc
Fasting	36	106.1	16	102.6
1 hour	36	195.3	16	161.7
2 hours	36	178.9	16	114.8
3 hours	36	135.6	16	91.8

we found, with few exceptions, normal values, and the average of the 36 blood sugar values after fasting was 106.1 mg. The temperature of 25 of the 36 patients ranged from 99 to 103 F. when the first test was made. At this time their blood sugar after fasting averaged 104.9 mg per hundred cubic centimeters. Eleven patients whose temperatures were normal (approximately 98.6 F.) at the time of the infection had an average blood sugar value after fasting of 109 mg per hundred cubic centimeters. It seems obvious, therefore, that infection and elevated body temperature per se do not consistently result in a fasting hyperglycemia.

The 9 cases of nonpyogenic febrile infections reported in table 3 yielded abnormal blood sugar curves. Case 43 (tertian malaria) showed a normal glycemic curve when the test was repeated after the patient had recovered. The blood sugar values after fasting were normal throughout.

Table 4 contains data on 28 patients with arthritis and rheumatoid conditions, 15 of whom (53.6 per cent) gave high and prolonged blood sugar curves.

TABLE 3—*The Effect of Nonpyogenic Febrile Diseases on the Tolerance for Dextrose*

Case	Age	Sex	Urea Nitrogen, Mg per 100 Cc	Temper- ature, F	Dextrose Tolerance Test					Bacteriologic Examination	Diagnosis
					Average Blood Sugar, Mg per 100 Cc			Urine Sugar			
					Fasting	1 Hr	2 Hrs		3 Hrs		
37	27	M	10.1	98.5	105	147	138	112	Negative	Negative	Pleuritis with effusion (convalescent period)
38	35	F	32.0	98.6	111	230	160	80	Negative	Blood culture negative	Typhoid fever, acute glomerulonephritis
39	32	M	10.0	99.4	95	187	174	87	Negative	Tubercle bacilli	Acute pulmonary tuberculosis, pleurisy
40	38	F		99.0	106	200	159		Negative		Active pulmonary tuberculosis, paroxysmal hypertension
41	17	F	9.0	103.0	108	200	190	160	Negative	Tubercle bacilli (sputum)	Tuberculous pneumonia
42	41	M	8.0	102.1	111	182	192	150	Negative	Tubercle bacilli (sputum)	Tuberculous pneumonia
43	24	M	9.0	100.0	111	204	169	142	Negative	Malarial para- sites (blood)	Tertian malaria
			13.0	98.5	95	125	121	100	Negative		One week later
44	31	M	11.0	100.9	101	198	170	147	Negative		Malaria
45	42	M	11.0	99.4	114	260	142	74	+		Urthritis (toxic), chronic infection in tonsils

TABLE 4—*Arthritis and the Tolerance for Dextrose*

Case	Age	Sex	Urea Nitrogen, Mg per 100 Cc	Temperature, F	Average Blood Sugar, Mg per 100 Cc				Urine Sugar	Diagnosis
					Fasting	Average Blood Sugar, Mg per 100 Cc		3 Hrs		
						1 Hr	2 Hrs			
46	55	M	15.0	101.4	125	263	274	200	Trace	Acute infectious arthritis, sinusitis, oral sepsis
47	35	M	13.0	98.6	100	167	187	127	Negative	Thirteen weeks later, clinically improved
			12.0	98.5	103	215	189	95	Negative	Rheumatoid arthritis, chronic infected tonsils, caries
48	78	M	6.6	98.6	111	213	190	105	Negative	Four weeks later, clinically improved
			13.0	98.7	87	200	118	105	Negative	Chronic multiple infectious arthritis, infected tonsils, coloptosis
49	43	F	16.0	98.6	89	238	116	102	Negative	Fifteen weeks later, clinically improved
			6.5	98.8	93	134	125	88	Negative	Infectious arthritis, acute tonsillitis
50	46	M	16.7	98.4	91	211	247	250	Negative	Four weeks later, clinically improved
			16.3	98.8	95	225	202	147	Negative	Infectious arthritis, chronic infected tonsils
51	15	M	7.5	99.8	102	200	269	118	Trace	Multiple infectious arthritis
52	27	F	9.0	98.7	100	125	108	111	Negative	Infectious arthritis, chronic tonsillitis, caries, Riggs' disease
53	37	F	53	99.4	89	118	119	100	Negative	Infectious arthritis, chronic infected tonsils sinusitis
54	34	F	9.0	100.2	125	250	250	199	+ 2d hour	Infectious arthritis, chronic tonsillitis, caries pyorrhea
55	34	F	13.2	98.4	104	149	125	125	Negative	Infectious polyarthritis, pyorrhea, infected tonsils gingivitis
56	32	F	10.0	98.4	97	250	275	155	++ +	Acute infectious arthritis in right hip, chronic infected tonsils
57	23	M	18.8	100.0	91	121	93	74	Negative	Acute arthritis, searata
58	30	M	11.5	98.5	91	121	93	74	Negative	Acute multiple arthritis, anal fistula
59	41	M	6.0	98.6	83	140	109	166	Negative	Acute infectious arthritis
60	70	M	11.0	99.1	125	180	200	138	Trace	Multiple infectious arthritis, chronic infected tonsils
61	61	M	8.0	98.2	91	241	217	190	++ +	Chronic infectious arthritis, infected tonsils, old cardiac infarction
62	59	M	8.6	98.4	87	154	168	167	Trace	Chronic multiple arthritis, renal calculi, chronic cystitis
63	32	M	4.8	98.7	91	142	160	130	Trace	Periarthritis of shoulder and knee, gingivitis
64	52	M	15.0	98.9	105	217	167	107	Negative	Chronic gonorrheal arthritis multiple arthritis
65	21	M	15.8	99.4	100	116	108	92	Negative	Syphilitic arthritis of knee, hallux valgus
66	54	M	13.3	98.5	91	153	125	116	Negative	Arthritis of the spine
67	34	M	8.3	98.4	100	174	125	111	Negative	Tuberculous arthritis of knee, tuberculous testicle, pulmonary tuberculosis
68	48	M	9.4	100.0	95	169	154	118	Negative	Acute rheumatic fever (exacerbation), infected teeth
69	34	M	8.6	99.0	111	200	160	95	Negative	Acute rheumatic fever, caries, pyorrhea alveolaris
70	34	M	101.0	111	177	121	100	91	Negative	Acute rheumatic fever
71	28	M	12.8	98.6	101	186	119	91	Negative	Acute rheumatic fever, chronic infected tonsils, sinusitis
72	34	M	9.0	98.5	100	136	118	91	Negative	Acute articular rheumatism, chronic prostatitis
73	23	M	15.0	100.6	111	175	153	138	Negative	

Thus, while the average blood sugar level during the course of the dextrose tolerance tests did not rise above the maximum normal limit, although it did in individual cases, the average blood sugar value at the two hour interval was distinctly above normal (161.8 mg). This abnormality in carbohydrate tolerance is in accordance with the findings of Pemberton¹¹ and other students of arthritis. The blood sugar values after fasting were normal, averaging 100.1 mg per hundred cubic centimeters. Glycosuria (from traces to 4 plus) was noted in 8 cases during the tests.

From the fact that a patient usually shows a diabetic-like response of the blood sugar to the ingestion of dextrose, frequently with glycosuria, during an infection and a normal response on recovery, a diagnosis of diabetes from data on dextrose tolerance should be made with considerable circumspection until the influences of infection, if any, are entirely eliminated. In addition definite conclusions can hardly be drawn

TABLE 5—*Average Blood Sugar Values for Each Test Interval in Cases of Arthritis*

Time	Number of Determinations	Average Blood Sugar, Mg per 100 Cc
Fasting	28	100.1
1 hour after dextrose	28	179.3
2 hours after dextrose	28	161.8
3 hours after dextrose	28	126.3

until confirmatory evidence is secured from a second tolerance test performed after the patient has recovered.

In a study of the chemistry of the blood in diseases of the skin Schamberg and Brown⁹ noted a tendency toward an increased concentration of nonprotein nitrogen, urea nitrogen and uric acid in eczema and generalized pruritus. As an incidental matter of interest we made determinations of urea nitrogen on the filtrates of a majority of the blood specimens after fasting. Whether the infection was pyogenic, febrile or arthritic, the values for the blood urea nitrogen were well within normal limits, with but 3 exceptions, cases complicated by lobar pneumonia (case 18), toxic nephritis (case 19) and glomerular nephritis (case 38).

COMMENT

From the data presented in this article and those available in the current literature, it can be stated definitely that infection, whether pyogenic, nonpyogenic febrile, arthritic or, in many cases, dermatologic, results in a definite disturbance in carbohydrate metabolism or at least in the rate at which the sugar is removed from the blood stream. The exact cause of this alteration in the carbohydrate mechanism or the way in which this change is brought about is not definitely known. It

seems obvious, however, that this type of hyperglycemia is an associated phenomenon rather than an etiologic factor in the production of the infection. In a recent paper MacBryde⁵⁸ emphasized the occurrence of relative resistance to insulin in uncomplicated diabetes mellitus. In addition he enumerated other types of resistance to insulin, such as infection, destructive pancreatic disease, disorders of other endocrine glands, hepatic disease, acidosis, coma, diseases of the skin and cardiac decompensation. Himsworth⁵⁹ expressed the belief that insulin is secreted by the pancreas in an inactive form which requires activation by some unknown substance for which he tentatively proposed the name "insulin kinase." This activating substance, he concluded, is produced in the liver.

Somerford²⁰ noted a greater abnormality in glycemia curves in the types of eczema in which an exudation is present in the epidermis. He concluded that the hyperglycemia is due to the absorption of epidermal products present in the cutaneous exudate. Williams and Dick²⁵ concluded that the islands of Langerhans are injured in infectious and febrile diseases, resulting in a decreased production of insulin. Sweeney²⁸ also suggested that infectious toxemia suppresses the endogenous production of insulin. Downie²⁹ concluded that the disturbed tolerance for dextrose may possibly arise from a disordered insulin-epinephrine balance, but more likely from a disturbance of the glycogenic function of the liver and suppression of the endogenous production of insulin. As far as arthritis is concerned, Pemberton⁴⁴ stated that this phenomenon is primarily mechanical, being due to a failure of the blood to reach certain tissues adequately, especially the muscles. We have no new information to add to this interesting phase of the question except to point out that our highest curves were generally obtained in the types of pyogenic infections usually included under cellulitis.

SUMMARY

Seventy-three cases of infection have been subjected to the dextrose tolerance test. Among these were 36 cases of pyogenic infections, of which 18 were studied both during and after the infection, 9 of non-pyogenic febrile conditions and 28 of arthritis and rheumatism.

Among the 36 patients with pyogenic infection 29, or 72 per cent, gave distinctly pathoglycemic curves. The highest curves were obtained in cellulitis, the blood sugar on several occasions rising above 300 mg and usually remaining elevated over three hours after the ingestion of dextrose. Despite such high blood sugar values, far above the generally

58 MacBryde, C. M. Insulin Resistance in Diabetes Mellitus, *Arch. Int. Med.* 52: 932 (Dec.) 1933.

59 Himsworth, H. P. *Lancet* 2: 935, 1932.

accepted normal threshold of 180 mg, glycosuria was present in but 4 cases. When the infection had disappeared and the patient was ready to go home a second tolerance test almost invariably resulted in a normal blood sugar curve. Any previous tendency toward glycosuria had now disappeared.

Both streptococcic and staphylococcic organisms were effective in producing disturbances in the carbohydrate mechanism.

The 9 patients with nonpyogenic febrile conditions also yielded abnormally prolonged blood sugar curves.

Among 28 patients with arthritis and rheumatoid conditions 15, or 53.6 per cent, gave diabetic-like blood sugar curves.

The blood sugar values after fasting in pyogenic, nonpyogenic febrile and arthritic conditions were, with few exceptions, well within normal limits.

With 3 exceptions, cases in which obvious renal complications were present, the blood urea nitrogen level was within normal limits during the various infections.

CORRECTION

FURTHER OBSERVATIONS ON THE EFFECT OF DRUGS ON INDUCED
CARDIAC STANDSTILL EFFECT OF EPINEPHRINE AND
RELATED COMPOUNDS," M. H. NATHANSON, M.D.,
ARCH. INT. MED. 54: 111 (JULY) 1934

The legend for figure 4 (page 118), beginning with the second sentence, should read: *B*, *C* and *D* were taken after the intravenous injection of 0.2 mg. of 1-epinephrine. *B* shows a maximum rate of 100 with multiple rhythmic foci. *E* was taken twenty-five minutes after the injection.

In the legend for figure 7 the figure referred to in the last line is 4 rather than 8.

Book Reviews

The Science of Radiology Authorized by the American Congress of Radiology
Edited by Otto Glasser Pp 450 Springfield, Ill Charles C Thomas,
Publisher, 1933

One of the duties of Bryon Hubbard Jackson as Chairman of the Committee on History and Education of the American Congress of Radiology was the editing of a book which would denote the outstanding features developed in the science of roentgenology from the time of Roentgen's discovery to the period of the Congress. Dr Jackson's happy choice of editor was Otto Glasser, the director of the Radiation Research Department of the Cleveland Foundation. The result is a well edited and, considering its scope, a fairly comprehensive outline of the field it attempts to cover. Charles C Thomas is the publisher, and the quality of design is up to his usual high standard.

The first two chapters of the book are by Otto Glasser and deal with the lives of Roentgen and of Pierre and Marie Curie and with the discoveries of the roentgen rays and radium. Then follow chapters on physics, apparatus, recording mediums and screens, dosimetry, diagnosis and so on. The list of contributors, in addition to the editor, includes the following: William Evans, David Webster, E C Jerman, William Collidge and E E Charlton, Arthur W Fuchs, J Camer Hudson, Percy Brown, Willis F Manges, Hans A Jarre, Ursus V Portmann, Gioacchino Failla and E H Qumby, Harry H Bowring and Robert Fricke, George M MacKee, Hermann J Muller, Charles Packard, Lauriston S Taylor, James T Case, George Clark, Edward Skinner, Matthew Luckiesh, Arthur H Compton and William Seifriz.

The Spread of Tumors in the Human Body By Rupert A Willis **Mono-**
graphs of the Baker Institute of Medical Research Number 2 Price,
25 shillings Pp 540 London J & A Churchill, 1934

Dr Willis receives the reviewer's enthusiastic praise for having produced a truly monumental work. Every physician has been intrigued by the natural history of the growth of tumors and has realized, more or less vaguely, that there are laws which govern the mode of spread of various neoplasms in the human body. But while most are familiar with the cruder facts, such as the frequency of metastasis to bone from cancer of the breast or prostate and the infrequency of deposits in bone from cancer of the stomach, no accurate source of information has been available on the more intimate details of these matters. The author leaves no nook or cranny of the subject unexplored, indeed, one admires his penetrating curiosity almost as much as the results of the researches. Furthermore, this monograph serves as an example of scholarly methods. Every statement is documented, and there is a bibliography of more than two thousand titles. Above all, the style of writing has that charm which is essential in relieving the monotony which otherwise attends a subject largely statistical. The format is pleasing, and the illustrations are instructive. The reviewer ventures to predict that this book will take its place among the classics of medicine, he advises every physician of literary inclination to secure a first edition.

Acute Intestinal Obstruction By Monroe A McIver **Hoerber's Surgical**
Monographs Price, \$7.50 Pp 340 New York Paul B Hoerber, Inc,
1934

After reading McIver's monograph one feels that there is nothing more to be said on the subject, if anything, the discussion has been almost too prolonged. Part 1 deals with the etiology, pathology and clinical features of the various types of obstruction. In part 2 diagnosis and treatment are considered, whereas part 3 is devoted to an analysis of the interesting problem of the cause of death. The writer seems specially qualified to deal with the whole subject, not only because of his clinical interests but because of his pioneer work with Gamble on the chemical derangements associated with intestinal obstruction. The unsurpassed format of the Hoerber monographs is maintained with a profusion of excellent illustrations, charts and diagrams. The bibliography is thorough, and there is a good index.

ACUTE DIFFUSE GLOMERULAR NEPHRITIS

STUDY OF NINETY-FOUR CASES WITH SPECIAL CONSIDERATION OF
THE STAGE OF TRANSITION INTO THE CHRONIC FORM

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During the past fifteen years intensive investigations of chronic nephritis have brought about remarkable changes in the conception of many of its features. The disturbances of mineral, protein and water metabolism and their relationship to symptoms as well as to histologic changes have been worked out in some detail. The studies of acute nephritis, especially in the adult, are comparatively few, and this disease is less well understood than the chronic form.

It is almost universally accepted that chronic glomerular nephritis develops as the result of an acute attack which remains unhealed. Yet no extended experience with the chronic form is necessary to show that in most cases a history of an acute attack is lacking. In many cases the acute attack is so mild that the disease passes unnoticed, and the first evidence of a damaged kidney appears months or years later with the development of the signs and symptoms of the chronic stage. If the prevailing opinion is accepted that acute diffuse glomerular nephritis is characterized by the sudden onset of hematuria, hypertension and edema, many cases of the acute form will continue unrecognized until they pass into the chronic phase. Such a classic picture of hematuria, hypertension and edema develops only after an abrupt attack of acute nephritis which, at least temporarily, overwhelms the function of the kidney. Milder attacks may produce no such syndromes, but are capable of producing a lesion which just as often leads to the chronic form. As has been pointed out by many writers, and especially stressed by Volhard,¹ Longcope and his associates,² Lyttle and Rosenberg³ and

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1 Volhard, F, in von Bergmann, G, and Stachelin, R. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol 6, p 2, p 1179.

2 Longcope, W T, O'Brien, D P, Guire, J M, Hansen, O C, and Denny, R R. Relationship of Acute Infections to Glomerular Nephritis, *J Clin Investigation* 5:7 (Dec) 1927.

3 Lyttle, J D, and Rosenberg, L. Prognosis of Acute Nephritis in Childhood, *Am J Dis Child* 38:1052 (Nov) 1929.

Bell and Hartzell,⁴ scarlet fever and severe streptococcic infections of the throat are considered the most important causes of acute glomerular nephritis. Yet milder grades of infections of the upper respiratory tract, which frequently are not suspected as etiologic factors, may produce severe nephritis. Occasionally the only evidence of an attack of nephritis is found on examination of the urine, and it may be missed unless urinalysis is repeated frequently. If specimens of urine were examined as carefully and as often during the course of all infections of the upper respiratory tract as during scarlet fever, many more cases of acute nephritis would be disclosed.

Following the acute attacks of either the severe or the mild form, there is often a period of quiescence, in which the renal lesion heals completely or passes insidiously into the chronic phase. It is in this stage of transition that the patient usually feels well and is often regarded as cured, and attention to the details of diagnosis and treatment is neglected. The result is that the patient lives comfortably, not knowing that anything has gone wrong with the kidney until the chronic form supervenes months or years later, when little or nothing can be done to stop the downward progress of the disease. While the disease is still in the transitional stage it is of great importance to be able to determine, in a given case, whether the acute nephritic lesion is healing or becoming chronic. There is good reason to believe that if the true course of the disease is known and vigorous treatment instituted in this stage, the unfavorable sequelae may be prevented, for it is at this period that chronic glomerular nephritis may become inevitable, and the destiny of the kidney is determined.

In this report special emphasis is laid on the less pronounced cases of acute nephritis and on those in the stage of transition. We have analyzed ninety-four cases of acute diffuse glomerular nephritis admitted to the clinic of the hospital and dispensary for the treatment of nephritis during the years 1924-1934. The patients admitted during the period from 1929 to 1934, however, were more completely studied, and their cases are more fully reported here. The purposes of this study are as follows: (a) to review the general features of our cases as they were seen chiefly in adults, (b) to show that during the course of mild infections such as the common cold, when special attention is paid to the urinary findings, unsuspected nephritis may be diagnosed, and that the classic syndromes of hematuria, hypertension and edema need not be present, (c) to give particular consideration to the cases in the stage of transition during which healing or a state of chronicity occurs, and, finally (d) to show that the blood urea clearance test and

⁴ Bell, E. T., and Hartzell, T. B. Etiology and Development of Glomerulonephritis, *Arch Int Med* 29:768 (June) 1922.

the sedimentation rate for erythrocytes in conjunction with the tests more commonly used, aid in deciding whether the renal lesion is healing or becoming chronic

ANALYSIS OF THE CLINICAL DATA

In this series there was wide variation in the age incidence, as shown in table 1, in which a comparison of the ages of the patients is given. It may be noted that fifty-nine of ninety-four cases, or 62.7 per cent, occurred in patients between the ages of 10 and 30 years, while in thirty-five cases the patients were past 30 years of age. The table emphasizes the fact that this is not a childhood group, but predominantly a series of adults with nephritis. Also, it is shown that of fifty-nine patients under 30 years of age, twelve or 20 per cent, died, as compared with fifteen, or 42 per cent, of thirty-five patients in the group over

TABLE 1—*Comparison of Ages of Ninety-Four Patients with Acute Glomerular Nephritis*

Age, Years	Number of Cases	Recovered		Became Chronic		Died	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
0 to 10	50	31	62.54	16	27.12	12	24.34
11 to 20							
21 to 30							
31 to 40	35	16	45.71	4	11.43	15	42.86
41 to 50							
51 to 60							
Total	94	47	50.00	20	21.28	27	28.72

30 years. Of twelve patients under the age of 10 years, seven recovered, the condition of three became chronic, and two died (table 2). Although acute glomerular nephritis may occur at any age, it is rare after the age of 50 and common in children and adolescents. The higher incidence among young patients is, without doubt, properly attributed to the greater frequency of diseases of the upper respiratory tract.

The sex of the patients appeared to be inconsequential. As shown in table 2, there were fifty-one males and fifty-three females. The age, sex incidence and final outcome are arranged according to decades.

It has been pointed out from time to time that the mortality rate is higher among adults with acute nephritis than in children. Our mortality rate was highest among the patients in the age group from 40 to 50 years, as six of twelve patients in this group died. Between the ages of 30 and 40 years, eight of twenty patients died, while in the age group from 20 to 30 years, four of twenty-one patients died. Twelve cases occurred in patients between 5 and 10 years of age, and of these two died. The outcome in relation to age and sex incidence is arranged in table 3. The average age of patients who died was

29 years, as compared with 20 and 24 years, respectively, for those in whom the condition became chronic or who recovered. Of the entire series of patients 47, or 50 per cent, recovered completely, in twenty, or 21 per cent, the condition became chronic, and 27, or 28 per cent, died.

The form of acute nephritis complicating scarlet fever has been taken as a model of acute diffuse glomerular nephritis. Twenty years ago scarlet fever was considered the chief cause of acute diffuse

TABLE 2—*Age and Sex Incidence in Ninety-Four Cases of Acute Glomerular Nephritis*

Age	Num ber	Per Cent of Total	Num ber of Males	Per Cent of Total	Num ber of Females	Per Cent of Total	Num ber Recov ered	Per Cent of Total	Num ber Became Chronic	Per Cent of Total	Num ber Died	Per Cent of Total
0 to 10	12	12.77	7	7.45	5	5.32	7	7.44	3	3.19	2	2.13
11 to 20	26	27.66	11	11.70	15	15.95	12	12.77	8	8.51	6	6.38
21 to 30	21	22.33	8	8.51	13	13.83	12	12.77	5	5.32	4	4.25
31 to 40	20	21.27	11	11.70	9	9.57	9	9.57	3	3.19	8	8.51
41 to 50	12	12.77	11	11.70	1	1.06	5	5.32	1	1.06	6	6.38
51 to 60	3	3.20	3	3.20	0	0	2	2.13	0	0	1	1.06
Total	94	100.00	51	54.25	43	56.38	47	50.00	20	21.28	27	28.72

TABLE 3—*Outcome in Relation to Age and Sex Incidence*

	Num ber	Per Cent of Total	Num ber of Males	Average Age of Males, Years	Num ber of Females	Average Age of Females, Years	General Average Age, Years	Young est Patient	Oldest Patient
Recovered	47	50.00	29	27.72	18	21.77	24.75	5	59
Became chronic	20	21.28	4	18.00	16	22.43	20.21	8	46
Died	27	28.72	19	34.57	8	23.50	29.03	7	57
Total number of cases	94	100.00	52	26.76	42	22.57	24.66	5	59

nephritis. More recently, however, investigations have shown that other forms of infections, especially those of the upper respiratory tract, overshadow scarlet fever as the chief cause of acute nephritis. As shown in table 4, fifty-four, or 57.4 per cent, of the cases were caused by the common cold, tonsillitis and pneumonia. The onset of acute nephritis was preceded by scarlet fever in only two cases. The infrequency of scarlet fever as an etiologic agent in this series is surprising, but we believe it may be explained by the fact that our cases were gathered in a general hospital to which few patients with contagious diseases are admitted.

At the head of the list of etiologic factors are the common cold and influenza. They accounted for twenty-six cases, or 27.6 per cent. Pneumonia occupies an important place in our list, for eight, or 8.5 per cent of our cases were caused by it. This comparatively high

incidence may be explained by the fact that we have carefully watched these patients for evidences of acute nephritis. We have excluded cases of so-called febrile albuminuria.

Within recent years the part played by the toxemia of pregnancy in the production of acute nephritis has been emphasized by various authors (Mussey and Keith,⁵ Bell⁶ and Baird and Dunn⁷). These writers have expressed the belief that acute glomerular nephritis is one of the manifestations of the toxemia of pregnancy. We have selected sixteen cases from among a large number of patients with eclampsia to illustrate the acute nephritic syndromes commonly observed. Our autopsy studies in connection with these cases lead us to believe that acute diffuse glomerular nephritis due to eclampsia is practically the same as that due to other causes.

TABLE 4—*Etiology of Ninety-Four Cases of Acute Glomerular Nephritis*

Causes	Num ber of Cases	Per Cent of Total	Num- ber Recov- ered	Per Cent of Total	Became Chronic	Per Cent of Total	Num ber Died	Per Cent of Total
Common cold, influenza	26	27.66	12	12.78	7	7.44	7	7.44
Cold (exposure)	1	1.06	1	1.06	0	0	0	0
Sore throat, tonsillitis	20	21.27	14	14.89	3	3.20	3	3.20
Scarlet fever	2	2.13	0	0	1	1.06	1	1.06
Pneumonia	8	8.51	2	2.13	2	2.13	4	4.25
Other infections	14	14.89	8	8.51	0	0	6	6.38
Toxemia of pregnancy	16	17.03	6	6.38	7	7.44	3	3.20
Unknown	7	7.45	4	4.25	0	0	3	3.20
Total	94	100.00	47	50.00	20	21.27	27	28.73

The five classic clinical syndromes which characterize the chronic stage of nephritis, as outlined elsewhere by one of us,⁸ are applicable to the acute phase. They are (a) the urinary syndrome, (b) hypertension, (c) edema, (d) retention of nitrogen and (e) uremia. As in the chronic stage, it is seen in the acute that not all the syndromes need be present at the same time, at times one or another develops and dominates the clinical picture and then disappears, to reappear at a later date or never to return. In every case the urinary syndrome was present when the diagnosis was made. Some authors, notably Kylin,⁹ have reported that hypertension, edema and even uremia may precede

5 Mussey, R. D., and Keith, N. M. Significance of Nephritis in Pregnancy, *J. A. M. A.* **91**:2044 (Dec. 29) 1928.

6 Bell, E. T. Renal Lesions in Toxemias of Pregnancy, *Am. J. Path.* **8**:1 (Jan.) 1932.

7 Baird, D., and Dunn, J. S. Renal Lesions in Eclampsia and Nephritis of Pregnancy, *J. Path. & Bact.* **37**:391 (Sept.) 1933.

8 Murphy, F. D. Syndromes of Chronic Nephritis and Their Corresponding Morphological Changes, *Internat. Clin.* **2**:45 (June) 1929.

9 Kylin, E. *Die Hypertoniekrankheiten*, Berlin, Julius Springer, 1926, p. 57.

albuminuria. We have never observed this. The urinary syndrome, as shown in table 5, was present in every case, and in many cases it was the only one present when the diagnosis was made. Reliance on the urinary changes was necessary to a great extent in many of our cases, because other classic syndromes, as edema, hypertension and retention of nitrogen, were absent. Disturbances of urination, characterized by frequency of micturition and oliguria or occasionally complete anuria, were foremost among the symptoms at the onset, and at times were the only symptoms present. It was necessary, occasionally, to differentiate between febrile albuminuria and genuine acute nephritis in some of the milder cases. Frequently simple albuminuria developed and continued during the period of high fever, while acute glomerular nephritis set in after the chief symptoms of the causal disease subsided. In cases of febrile albuminuria, few or no red blood cells, pus cells and granular casts were found, while in nephritis these elements were prominent features. Changes in the urinary output, as oliguria or anuria, were rarely present in febrile albuminuria and were constant in nephritis. Also, in febrile albuminuria the albumin diminished rapidly with the subsidence of fever, but in acute nephritis the urinary syndrome continued for weeks after the fever disappeared. The amount of albumin excreted in twenty-four hours was so variable that we concluded that little or no significance could be attached to the quantity passed in the acute cases. Likewise, hematuria varied greatly, not only from patient to patient, but from day to day in the same patient. In some cases the urine was bloody from the onset, while in others only an occasional red cell was found during the acute stage. From such experiences we do not believe, as some advocate, that the term acute hemorrhagic nephritis should be used synonymously with acute diffuse glomerular nephritis. Gross hematuria was present in thirty-six cases, or 38 per cent. Red blood cells were in the sediment in varying amounts at some period of the acute process in every case. However, the number of red blood cells and of casts or the amount of albumin bore no relationship to the severity of the disease. Some of our cases in the early stages showed pronounced hematuria, and so were diagnosed as cases of focal glomerular nephritis, but we found on further observation that genuine diffuse glomerular nephritis existed.

Table 5 shows that hypertension was present in seventy-four cases, or 78.7 per cent. Its presence or absence did not appear to influence greatly the ultimate outcome. Rising blood pressure or hypertension that tends to persist after other signs have subsided is an unfavorable sign. Our observations tend to substantiate the opinion that persistent hypertension is indicative of an unhealed nephritic lesion. Cerebral hemorrhage is thought to be rare in acute nephritis, yet in this series it occurred twice. In each case the blood pressure was only moderately elevated, and the patients were under 20 years of age.

Associated at times with hypertension are changes in the fundus oculi. In this series neuroretinopathies were found in only seven patients with excessive hypertension. Frequently, the excessive hypertension was complicated by convulsions. The changes in the eyegrounds varied from lesions of mild degree, characterized by slight retinal edema and moderate constriction of the retinal arteries, to the typical picture of so-called nephritic retinitis, consisting of edema of the retina, choked disks, hemorrhages along the course of the retinal arteries, narrowed and partially obscured retinal arteries and white patches. Although some observers, as Fishberg,¹⁰ have pointed out that the presence of nephritic neuroretinopathy indicates a serious prognosis, we cannot

TABLE 5—*Syndromes Occurring in Ninety-Four Cases of Acute Glomerular Nephritis*

Syndromes	Recovered (47)		Became Chronic (20)		Died (27)	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Urinary	47	100.00	20	100.00	27	100.00
Hypertension	35	74.47	15	75.00	24	88.80
Edema	32	68.09	15	75.00	15	55.55
Retention of nitrogen	31	65.96	13	65.00	23	85.19
Uremia	6	12.77	2	10.00	20	74.07
Genuine	0	0	0	0	14	51.85
Convulsive	6	12.77	2	10.00	6	22.22

TABLE 6—*Causes of Death in Twenty-Seven Cases of Acute Glomerular Nephritis*

Causes	Number of Cases	Per Cent
Uremia	20	74.07
Heart failure	3	11.11
Pneumonia	3	11.11
Other infections	1	3.71
Total	27	100.00

reach that conclusion from our observations, as some of our most dramatic recoveries were among the patients having convulsions and neuroretinopathies.

Various degrees of myocardial insufficiency were found in fifteen of the ninety-four cases observed, and, as seen in table 6, in three of the twenty-seven fatal cases death was caused by heart failure. Failure of the left ventricle was observed in these cases, and was usually associated with excessive hypertension and convulsions. During the convulsion the heart was frequently observed to be on the verge of collapse, only to return to a normal state with recovery from the convulsive attack. As emphasized by Levy,¹¹ hypertension frequently causes mild

¹⁰ Fishberg, A. M. Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934.

¹¹ Levy, I. T. Cardiac Response in Acute Diffuse Glomerular Nephritis, *Am. Heart J.* 5:279 (Feb.) 1930.

degrees of heart failure, which often pass unnoticed. Although heart failure in our group usually was associated with hypertension, this was not always true. In one fatal case the blood pressure was not elevated, yet the patient died of failure of the left side of the heart. A report of this case is given because it illustrates several features we wish to emphasize: first, that left ventricular failure may occur in acute nephritis with no elevation of the blood pressure; second, that in acute diffuse glomerular nephritis there may be too few red blood cells in the urine to warrant the term "hemorrhagic," and, finally, that acute glomerular nephritis may set in rapidly following exposure to cold and the onset of an infection of the upper respiratory tract.

CASE A—A white man, aged 33, a city fireman, entered the hospital on Aug 8, 1933. He had always been in splendid health. On August 4, he was drenched with water, and a severe cold developed in the head and chest. He was confined to bed on August 6 and 7. On August 8, he felt worse, and had not urinated for twenty-four hours. On catheterization about 15 cc of clear urine was obtained. Analysis revealed albumin 4 plus, from 8 to 10 pus cells, 8 to 10 granular casts and from 2 to 4 red blood cells per field. The nonprotein nitrogen was 210 mg per hundred cubic centimeters and the creatinine was 14 mg. The blood pressure, which had always been normal, was 132 systolic and 90 diastolic. Efforts to bring about diuresis failed. On August 9, he became dyspneic, and râles began to gather in the bases of both lungs. During the day the signs of left ventricular failure became more pronounced, and toward evening well developed pulmonary edema with the typical frothy expectoration set in. The blood pressure dropped to 100 systolic and 70 diastolic, and a definite gallop rhythm developed. Complete anuria persisted. Heart failure rapidly increased in severity, and the patient died the next morning.

At autopsy the kidneys were large, white and smooth, the right one weighing 225 Gm and the left, 195 Gm. The capsules stripped with ease, and the renal substance bulged out through the opening made in the true capsule. No hemorrhagic areas were seen on opening the kidney. Microscopically the glomerular tufts were uniformly enlarged, practically filling Bowman's space in most areas. The capillaries of the tufts were practically bloodless throughout. The lumens were occluded by swelling of the endothelial cells and polymorphonuclear leukocytes. The endothelial cells of the capillaries were considerably increased in number in some sections, in others this was not so noticeable. In the capsular spaces, exudate containing pus cells but no red blood cells had accumulated. The epithelial cells of the proximal and distal convoluted tubules were swollen, and appeared to be undergoing granular degeneration. Very little fat was found with the fat stains, and no doubly refracting lipoids were seen with the polarizing microscope. The blood vessels were normal.

Every patient in our series having uremia of the convulsive type had hypertension before convulsions set in. As a rule the blood pressure was higher in these cases than in others, and convulsions developed at the height of the pressure. The association of hypertension and the onset of convulsions is so striking that we believe a cause-and-effect relationship exists.

Edema was never a severe complication in this group of cases. Usually it was slight, with puffiness about the eyes, occasionally it was more pronounced, with ascites and fluid in other cavities, but it rarely assumed the proportions of generalized anasarca. Edema developed in sixty-two cases, or 65.9 per cent. It was present in thirty-two, or 68.09 per cent, of the patients who recovered, while it occurred in fifteen, or 75 per cent, of those in whom the condition became chronic and in fifteen, or 55.5 per cent, of those who died. There was no relationship between the degree of edema and the prognosis. As shown in table 5, edema was least often present in fatal cases and most often in those becoming chronic. In many of the cases studied the amount of plasma proteins was determined. There seemed to be no relationship between the quantity of plasma protein and the edema, as is so marked a feature of chronic nephritis with edema. In most cases the amount of total protein and of albumin and globulin was normal. In most cases with edema the plasma protein level was normal, occasionally edema was associated with a reduction of the total plasma protein to 6 Gm. per hundred cubic centimeters or below, with an albumin level between 3 and 4 Gm. per hundred cubic centimeters. Rarely, a decrease of protein was found when no edema prevailed.

Estimations of the blood cholesterol content were done in seventy-two of the ninety-four cases. In eighteen cases there was a cholesterol content above 200 mg. There was no relationship between the content of blood cholesterol and the fatal outcome. In the group whose condition became chronic there was a tendency of the content of the blood cholesterol to rise gradually. Retention of nitrogen was present in sixty-seven cases, or 71.2 per cent. When anuria set in suddenly the rise in nonprotein nitrogen usually occurred promptly. The degree of retention of nitrogen did not alter the prognosis, but with an elevated nonprotein nitrogen value that remained higher than normal the outlook for complete recovery was unfavorable. An initial abrupt rise in nonprotein nitrogen was frequently followed by prompt recovery, while other cases with little or no rise in the blood nonprotein nitrogen ended fatally. A rising nonprotein nitrogen level, as shown by repeated examinations, indicated a failing kidney and a poor prognosis.

The uremia syndrome occurred in twenty-eight cases, or 29.7 per cent. In this analysis the term uremia was used to embrace two rather different clinical syndromes. Although such use of the term uremia may not be acceptable to all, it has long been used in the sense in which it is employed here. Two forms of uremia were recognized, the genuine form and the convulsive or so-called false uremia of some writers. The convulsive form occurred in six, or 12.7 per cent, of the patients who recovered, in two, or 10 per cent, of those with conditions becoming chronic, and in six, or 22.2 per cent, of those who died. This form

was always associated with hypertension, headache and visual disturbances, and frequently was accompanied by edema. Temporary blindness was seen to come on before or during the attack and rapidly clear up with the subsidence of hypertension. The hypertension is believed to be the chief cause in this type. The retention of nitrogen and anuria appeared to be unrelated to this form of uremia. The hypertension already present rose sharply before the attack. As a rule, those with convulsive uremia alone recovered. When anuria or oliguria developed, a combination of genuine and convulsive uremia was seen to occur. In sharp contrast to the convulsive form is the genuine or true uremia. This form needs no explanation here, as it is the direct result of renal insufficiency. Genuine uremia occurred in fourteen cases, and death followed in each instance (table 5). These were cases in which renal failure developed, and treatment failed to bring about diuresis.

Although the five classic syndromes of nephritis characterize the acute as well as the chronic stage of glomerular nephritis, all except the urinary syndrome may be absent, especially in the earlier stages and in milder forms of the disease. Not all the syndromes may be present at one time, sometimes one or the other appears and dominates the picture for a while and then disappears, to reappear at some later date or never to return at all.

STAGE OF TRANSITION

When the acute attack is severe, the diagnosis, clinical course and treatment are usually well defined. But after the acute phase is over, which usually occurs within a period of six weeks, the problem frequently arises as to whether the renal lesion has completely healed or has subsided temporarily, only to progress into the chronic stage later on. Acute diffuse glomerular nephritis may take several courses: 1. The patient may die in the acute attack. 2. Chronic nephritis may develop. 3. Complete healing may occur. 4. Albuminuria may persist in small quantities for years, although the patient may be clinically cured. This is called latent albuminuria. We know that the severity of the acute attack has little influence on the subsequent course, as in some of the most severe attacks of acute nephritis healing occurred promptly, while a mild attack might be followed shortly by the chronic stage. In the type of case with a poorly defined acute stage, with symptoms so mild that they rarely attract attention, the condition of the patient who usually feels quite well may pass unrecognized and untreated into the healed stage, or progress insidiously into the chronic form.

It is in the period of transition from the acute attack into the healed stage on the one hand and into the chronic phase on the other that the ultimate fate of the patient is determined. Our experience with

this series of cases leads us to believe that the danger of oncoming chronic nephritis may be recognized in this transitional stage and that more vigorous and prolonged treatment may bring about complete quiescence of the disease. The knowledge at least of the presence of the unhealed lesion is of considerable importance, as it leads to more caution in avoiding mild infections and to more diligence in treating them. A sense of false security may develop during this time because of the patient's apparent well-being, and ordinary tests show the kidneys to be well on the road to complete healing. At times, in spite of the most careful examinations, it is difficult to decide whether the renal lesion is healing or becoming chronic. In some cases, the chronic form appears many years after all the ordinary tests indicated that healing was taking place.

The functional tests more commonly used, such as the phenol-sulphonphthalein test, and the degree of retention of nitrogen have not helped greatly in deciding this question. Such tests are of value when the renal function is decidedly reduced. In cases of the type under consideration more delicate tests have been shown to be of greater value. The functional tests show only the degree of loss of reserve capacity of the kidneys, and do not indicate whether or not an inflammatory lesion persists. It seems possible for a pathologic lesion to be active in the kidney and to be associated with normal function. In attempting to determine the degree of activity of the inflammatory lesion in these transitional cases, we have found that no test alone is a reliable guide in every case.

Several methods have been used in approximating this information, and we found that a combination of these results forms a more adequate prognostic indication than any test taken alone. The blood pressure, a study of the urinary sediment, the degree of anemia, the amount of plasma proteins and the dilution concentration test of Volhard, in general, have been of considerable value, but the blood urea clearance test and the sedimentation rate of the erythrocytes have been of particular help. These measures will be presented seriatim, and the last two will be discussed more fully than the rest, because they have been found to be the most accurate of all in estimating the degree of activity in the renal lesion.

1. An elevation of the blood pressure indicates active glomerular damage. Normal pressure, however, does not signify a healed lesion, for some patients, especially those with a mild attack, have no rise in blood pressure.
2. Gradually diminishing albuminuria points toward a healing process. But in some cases there was a mere trace of albumin, and subsequently chronic nephritis developed. The number of red blood cells and granular casts in the sediment makes a more reliable guide. A decrease in the number of these elements points toward healing, but occasionally the sediment may contain no

cells, and yet the chronic phase may ensue 3 Anemia (below less than 3,500,000 red blood cells) implies a progressive renal breakdown, but this is an unreliable guide, for anemia practically never appears in mild cases 4 A fall in the plasma protein values is a sign of a progressive renal lesion, while if the plasma protein values remain normal the case usually progresses satisfactorily It was observed that the decrease was not commensurate in all cases with the amount of protein in the urine, other factors appear to influence the plasma protein values 5 The concentration and dilution test of Volhard was found to be very reliable Impaired concentration in most cases pointed to an unhealed progressive lesion This important test requires considerable cooperation from the patients, however, we have found it to be of great help in arriving at a proper prognosis 6 Of all tests the blood urea clearance was the most accurate, yet, in a few cases it was found to be undependable 7 Finally, the erythrocyte sedimentation rate proved to be an important aid in determining the degree of activity of the renal lesion In this series we have paid particular attention to the last two tests, and therefore we shall discuss them more fully than the others Summaries of the data on all the cases which became chronic are given in table 7, and similar data are given in table 8 on ten of the forty-seven cases which went on to recovery These ten were selected because on them we have been able to do more complete work and have a more adequate follow-up than on the others

The blood urea clearance test, as described by Moller, McIntosh and Van Slyke,¹² has been used regularly in the study of our cases A discussion of the technic of the test seems unnecessary, for, subsequent to the original description, it has been used widely and reported on by such workers as Van Slyke, McIntosh, Moller, Hannon and Johnston,¹³ Cantarow and Ricchiuti¹⁴ and Bruger and Mosenthal,¹⁵ all of whom have given detailed descriptions of the procedure In this report the figures for blood urea clearances are given in a per cent of the normal mean, which, according to Van Slyke and his associates, is 54 cc of blood per minute for the normal average standard clearance and 75 cc

12 Moller, E, McIntosh, J T, and Van Slyke, D D Studies of Urea Excretion II Urine Volume and Rate of Urea Excretion by Normal Adults, *J Clin Investigation* 6 427 (Dec) 1928

13 Van Slyke, D D, McIntosh, J F, Moller, E, Hannon, R R, and Johnston, C Studies of Urea Excretion VI Comparison of the Blood Urea Clearance with Other Measures of Renal Function, *J Clin Investigation* 8 357 (April) 1930

14 Cantarow, A, and Ricchiuti, G Urea Clearance Test in Pregnancy, *Arch Int Med* 52 637 (Oct) 1933

15 Bruger, M, and Mosenthal, H O Urea Clearance Test as an Index of Renal Function I Studies of Normal Subjects, *Arch Int Med* 50 351 (Sept) 1932

TABLE 7—Essential Data in Twenty Cases of Acute Glomerular Nephritis Which Became Chronic

Case	Age	Sex	Ethology	Date	Urinary Observations			Blood Chemistry					Blood Pressure		Edema	Uremia	Clearance	Sedimentation Rate	
					Albumin	Red Blood Cells	White Blood Cells	Casts	Specific Gravity	Non protein Nitrogen, mg per 100 Cc	Creatinine, mg per 100 Cc	Cholesterol, mg per 100 Cc	Systolic	Diastolic		Convolutions	Urea	1st Hour	2d Hour
1	16	F	Tonsillitis	12/28/32	+++	+++	++	+	1 016	34.8	1.5	320	128	88	+++	Neg	47	27	58
2	23	F	Sore throat, tonsillitis	3/29/33	+++	+++	+	0	1 011	38.2	1.6	355.4	150	80	+++	0	27	13	30
3	32	F	Toxemia of pregnancy	7/9/26	+++	+++	+	0	1 030	31.08			90	55	0				
				8/23/26	+++	+++	+	0					188	98	0				
				7/9/32	+++	+++	+	0	1 018	40.3	1.9	230.0	162	104	+++	0	22	35	73
				11/1/32	+++	+++	+	0	1 018	47.2	1.8	220.3	200	140	+++	Convolutions	23	46	85
4	14	F	Common cold, influenza	11/8/30	+++	+++	+	Occ +	1 012	54.0	1.9	227.0	154	88	+++	0	15		
				7/13/31	+++	+++	+	+					140	100	+++		45		
5	16	F	Sore throat, tonsillitis	12/10/32	+++	+++	+	0	1 010	28.5	1.4	142.8	132	88	+++	0	44	19	24
6	13	F	Tonsillitis	4/2/33	+++	+++	+	+ Occ	1 008	27.7	1.5	238.1	132	80	+++	0	26	38	56
				7/13/31	+++	+++	+	+	1 015	39.5	1.5	189.3	148	100	+++	0	65	52	82
7	37	F	Toxemia of pregnancy	4/7/32	+++	+++	+	0	1 016	37.7	1.4	178.5	130	70	+	0	53	48	90
				6/20/33	+++	+++	+	+	1 024	45.4	1.4	400.0	200	120	+	0	56	42	81
8	17	M	Sore throat, tonsillitis	6/13/32	+++	+++	+	+++	1 017	33.7	1.6	200.0	190	115	+	0	32	16	37
				9/11/33	+++	+++	+	+	1 016	67.4	2.1	181.8	156	68	+	0	65	61	88
9	9	F	Pneumonia	3/18/33	+++	+++	+	+					155	90	+++		23		
				4/18/33	+++	+++	+	+	1 011	36.1	1.5	184.1	110	80	+++	0	38	21	50
10	20	F	Toxemia of pregnancy	5/7/32	+++	+++	+	+	1 019	33.0	1.5	181.9	150	100	+++	0	30	24	48
				3/6/33	+++	+++	0	+					145	120	+++				
11	24	F	Toxemia of pregnancy	1/1/30	+++	+++	+	+++					200	136	+	0		110	152
				10/2/33	+++	+++	0	+++					160	90					
12	8	M	Scarlet fever	2/7/25	+++	+++	+	+					132	92	0				
				6/12/25	+++	+++	+	+	1 022	52	2.4		121	90	0				
13	12	M	Sore throat, influenza	3/6/24	+++	+++	0	0	1 016				115	80	0				
				9/18/24	+++	+++	+	+	1 017	15	2.0	320	115	80	0				
14	22	M	Common cold, influenza	3/5/28	+++	+++	+	+	1 025	48	2.5	212	150	100	0				
				6/1/28	+++	+++	+	+	1 015	60	3.0	300	148	104	0		60	50	80
15	18	F	Pneumonia	11/7/30	+++	+++	+	0	1 018	42	1.8	190	142	100	0		45	38	63
				1/29/31	+++	+++	+	+	1 010	38	2.0		142	100	0			40	60
16	13	F	Sore throat, tonsillitis	7/3/26	+++	+++	+	+	1 028	32	1.2	220	110	80	0			50	75
				9/20/26	+++	+++	+	0	1 022	36	1.6	280	110	80	0				
17	38	F	Toxemia of pregnancy	4/12/32	+++	+++	+	+	1 024	40	2.8	310	190	115	+	0	32	28	50
				9/2/32	+++	+++	+	+	1 015	72	3.4		180	120	+	Convolutions	11	45	95
18	27	F	Toxemia of pregnancy	4/6/31	+++	+++	+	+	1 020				160	110	+	0	38	36	52
				8/20/31	+++	+++	+	+	1 010	60	3.0	216	142	92	+	0	26	42	88
19	19	F	Toxemia of pregnancy	2/2/27	+++	+++	+	0	1 024	46	2.1	200	158	100	+	0			
				5/10/27	+++	+++	0	+	1 018				160	100	+				
20	25	M	Tonsillitis, sore throat	10/12/31	+++	+++	+	+	1 025	25	2.0	184	140	85	+	0	38	40	65
				1/5/32	+++	+++	+	0	1 020	38	2.2	216	156	96	0		18	60	90

for the average maximum clearance. In determining whether the acute condition is healing or progressing into the chronic stage the blood urea clearance has definite value. It is probably the most delicate of any of the tests of renal function, and it reveals early functional impairment considerably sooner than the usual tests employed. Furthermore, it was pointed out by Van Slyke and his co-workers¹⁶ that one may interpret the blood urea clearance as a measure of the proportion of glomerular tissue still functioning and that a fairly accurate impression may be obtained concerning the rate of progress of the renal lesion itself. As shown in table 7, no case becoming chronic maintained a normal urea clearance. In a few, as in cases 1, 7, 8 and 15, the urea clearance was satisfactory during the early periods of the disease, ranging from 40 to 60 per cent of normal, while in others the initial observations revealed urea clearances as low as 10 per cent of normal. When the initial blood urea clearance was satisfactory in cases becoming chronic, repeated examinations showed a tendency toward a drop in the percentage, while in the cases in which the initial test showed a decided lowering of urea clearance ranging from 15 to 30 per cent of normal, a rise to normal was not found in the stage of transition into the chronic form. This does not mean that the percentage of clearance made no rise in some cases which became chronic. In case 4, for example, the initial clearance was 15 per cent, followed by a rise to 45 per cent, yet the condition continued toward the chronic stage.

In the group of cases which went on to the healed stage as a rule the urea clearances were depressed during the early periods of the acute stage, while in later periods the clearances tended to increase (table 8). In some, as in cases 22 and 28, the clearances were normal and remained so, but in most cases in this group an early depression showed, followed after several weeks of rather marked fluctuations by a gradual rise to normal. We wish to emphasize that clearance tests done during the early stages of acute nephritis do not tell whether the outcome will be favorable or unfavorable. However, repeated tests over a period of months show whether the general trend is toward healing or toward chronicity. This, nevertheless, is no ironclad rule, for there were cases in which the clearances remained normal during the early months, and yet the condition went on to the chronic stage, as seen in case 6, table 7. In this case the sedimentation rate was more serviceable as a prognostic guide than the blood urea clearance test. Because of its importance a more detailed presentation is given here.

16 Van Slyke, D. D., Stillman, E., Moller, E., Eggert, E. W., McIntosh, J. F., Leiter, L., MacKay, E. M., Hannon, R. R., Moore, N. S., and Johnston, C. Observations on the Course of Different Types of Bright's Disease and on the Resultant Changes in Renal Anatomy, *Medicine* 9:257 (Sept.) 1930.

TABLE 8—Essential Data in Ten Cases of Acute Glomerular Nephritis in Which Recovery Occurred

Case	Age	Sex	Etiology	Date	Urinary Observations				Blood Chemistry				Blood Pressure			Blood Urea		Sedimentation Rate		
					Albumin	Red Blood Cells		White Blood Cells	Casts	Specific Gravity	Non protein Nitrogen, mg per 100 Cc	Creatinine, mg per 100 Cc	Cholesterol, mg per 100 Cc	Edema	Systolic	Diastolic	Clearance	Urea	1st Hour	2d Hour
						Cells	Cells													
21	24	M	Common cold, influenza	12/14/32 3/30/33	++++ +	+++ 0	+++ 0	+++ 0	+++ 0	1.018 1.024	53 32	3.2 1.4	526.2 242.7	+++ 0	132 132	102 100	Neg Neg	23 50	15 12	60 18
22	40	M	Influenza, common cold	4/20/31 8/9/31	++++ 0	+++ ++	+++ ++	+++ ++	+++ ++	1.017 1.016	48 45	2.0 1.2		++ 0	120 120	70 80	Neg Neg	53 90	24 8	32 12
23	28	M	Sore throat, tonsillitis	9/1/31 10/24/31	++++ 0	++++ 0	++++ 0	++++ 0	++++ 0	1.016 1.020	96 39			0	112 120	80 80	Neg Neg	20 48	45 15	58 22
24	14	M	Sore throat, tonsillitis	10/3/33 12/15/33	++++ 0	++++ +	++++ +	++++ 0	++++ 0	1.018 1.024	43 30	1.5 1.4	162.3 183.2	++ 0	190 126	120 70	Convul sion	21 69	38 12	70 23
25	10	M	Tonsillitis, sore throat	11/14/33 2/18/34	++++ 0	++++ 0	++++ 0	++++ 0	++	1.013 1.018	54 30	3.0 1.8	138.0 151.5	++ 0	160 110	120 70	Neg Neg	12 52	9 8	25 18
26	33	F	Sore throat, tonsillitis	9/13/32 10/13/32	++++ 0	++++ 0	++++ 0	++++ 0	++	1.024 1.016	44 28	3.2 1.4		0	200 135	130 90	Convul sion	31 72	34 12	49 16
27	30	F	Toxemia of pregnancy	3/2/31 7/1/31	++++ Trace	++++ ++	++++ ++	++++ 0	++	1.016 1.020	56 34	2.8 2.1	290 184	++ 0	180 120	115 90	Neg Neg	24 68	40 8	55 15
28	7	M	Common cold, influenza	12/12/31 3/10/32	++++ 0	++++ 0	++++ 0	++++ 0	++	1.018 1.020	44 33			+++ 0	130 98	80 60	Neg Neg	45 105	24 18	31 32
29	16	M	Tonsillitis, sore throat	1/15/33 11/21/33	++++ +	++++ 0	++++ ++	++++ 0	++	1.013 1.021	40 35	2.2 2.6		+++ 0	150 120	105 80	Neg Neg	29 56	28 9	58 16
30	17	F	Tonsillitis	5/11/32 7/15/32	++++ 0	++++ 0	++++ 0	++++ 0	+++	1.017 1.024	67 43			++ 0	150 122	100 70	Neg Neg	17 55	10 10	68 21

CASE 6—A white schoolgirl, aged 13, was first observed on July 13, 1931, following an attack of tonsillitis three weeks previously. There was slight edema about the eyes, and urinalysis showed albumin 4 plus, many red blood cells and pus cells and a few granular casts. The blood pressure was normal, as well as the blood nonprotein nitrogen level and the reaction to the phenolsulphonphthalein tests. A blood urea clearance test was done repeatedly and gave values ranging from 65 to 75 per cent of normal. The erythrocyte sedimentation rate was 52 mm during the first hour and 82 mm during the second. After three weeks in the hospital the patient felt well and appeared to have made a complete recovery. A trace of albumin was found in the urine, with an occasional red blood cell and a few pus cells, but no casts. The blood pressure was normal, reactions to the tests of renal function were normal, the blood urea clearance was 70 per cent of normal. From the clinical as well as the laboratory standpoint she was making splendid recovery, and seemed to be progressing toward a healed stage. Had it not been for the rapid erythrocyte sedimentation rate of 54 mm during the first hour, we should have considered her quite well. During the next several months she seemed very well, and all tests pointed toward recovery with the exception of the rapid sedimentation rate. On Nov 6, 1932, edema reappeared, albuminuria became greater and the blood urea clearance test began to show a reduction in clearance for the first time. Although high blood pressure did not develop, the other syndromes of chronic glomerular nephritis gradually set in.

It is important, we believe, to stress that in dealing with cases in the transitional stage, the percentage of blood urea clearance may occasionally rise to normal figures, only to drop to below normal on subsequent tests. The opposite, too, may occur, an initial normal clearance may be followed by very low clearance, and subsequently there is a rise to normal, which level is maintained. An occasional estimation of the urea clearance, then, may lead one to false conclusions. Repetition, however, at regular intervals, over a period of several months, will show that in the healing stage clearances indicate a tendency to rise toward normal, while in those becoming chronic the tendency is toward a fall to decidedly low percentages.

Although the sedimentation rate of the erythrocytes has proved to be of value as an aid in the diagnosis and prognosis of many diseases, its use in nephritis has been sharply limited. As pointed out by Cutler,¹⁷ the test is not specific and is not a procedure for diagnosing any particular disease, but is to be used rather as a general symptom, like fever and leukocytosis, is used. First, it serves to indicate the presence of some disease in the body which is causing the breakdown of tissue, and, second, the test is a measure of the intensity of the disease process. As a diagnostic aid in nephritis we believe it is an unessential test, but as a prognostic guide, indicating the degree of activity present in the kidney, it has been of considerable value. In following the patient with acute nephritis through the transitional stage it has proved to be of

17 Cutler, A W. The Practical Application of the Blood Sedimentation Test in General Medicine, *Am J M Sc* 183 643, 1932

distinct aid in showing whether the renal lesion was going on toward healing or to chronicity. This is not an infallible guide in the stage of transition, for we have had patients with genuinely active acute glomerular nephritis in whom the sedimentation rate has been normal. In conjunction with the other tests it is a valuable aid.

The theoretical explanation of this phenomenon is at present not clearly understood. Most authors have expressed the belief that an increased agglutinability of the erythrocytes plays an important rôle, and that the suspension stability of the red blood cells is influenced by the fibrinogen and globulin content of the blood. Whenever the fibrinogen and globulin contents are increased, the sedimentation rate of the red blood cells becomes more rapid. The rapidity of the sedimentation is in direct proportion to the degree and extent of the destruction of tissue, or the progress of certain pathologic conditions. Klyn⁹ pointed

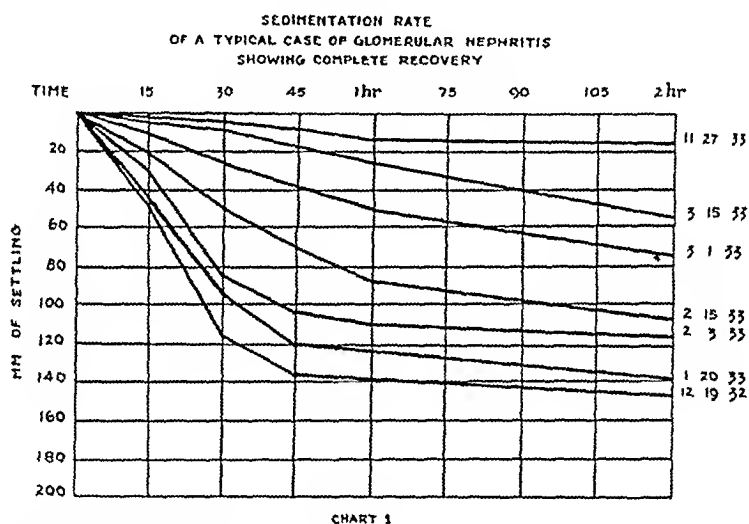


Chart 1—The sedimentation rate in a typical case of glomerular nephritis showing complete recovery

out that the changes in the plasma protein content play an important rôle in glomerular nephritis, producing an increased rate in the sedimentation of blood corpuscles, while in essential hypertension the stability of the plasma protein level is not affected and the sedimentation rate is normal.

We followed the original method of Westergren in studying the sedimentation rate of blood mixed with a 3.6 per cent solution of sodium citrate in a proportion of 1 part of sodium citrate to 4 parts of blood obtained by venipuncture. Into one of the special sedimentation pipets, which measures exactly 200 mm from the zero mark to the tip, 1 cc of citrated blood was taken up. The sedimentation of the red blood cells was measured at intervals of fifteen, thirty, forty-five and sixty minutes and two hours. The readings were plotted on graphs in each case, so that the progress or retardation of the sedimentation rate could be easily observed and compared.

The variations observed in the sedimentation rate in three typical cases of acute nephritis are shown by the graphs in charts 1, 2 and 3. Chart 1 shows a typical example of a case progressing satisfactorily to recovery, chart 2, a case resulting in death, and chart 3, a typical case which became chronic. Our observations with this test have led us to look on it as a fairly reliable gage of the progress of the renal lesion.

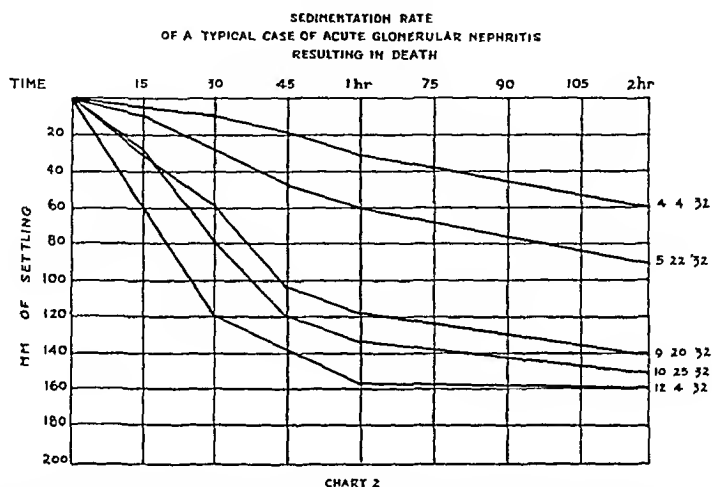


Chart 2—The sedimentation rate in a typical case of acute glomerular nephritis resulting in death

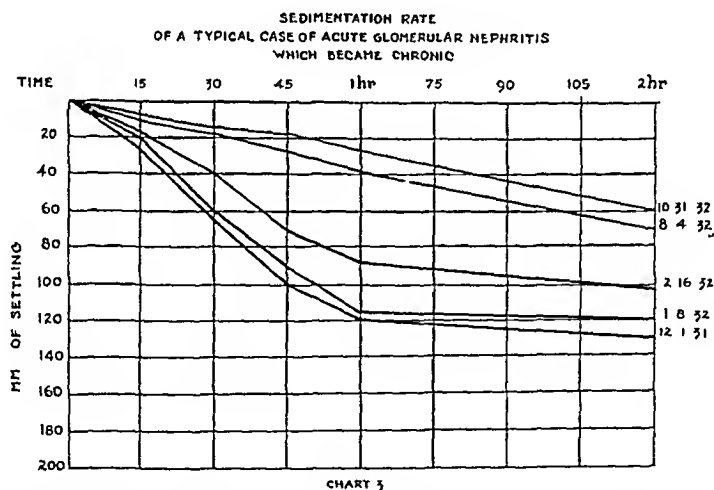


Chart 3—The sedimentation rate in a typical case of acute glomerular nephritis which became chronic

in the transitional stage. Our conclusions regarding the test may be given as follows: 1. In conjunction with the other tests enumerated, determination of the sedimentation rate is a valuable prognostic aid. 2. A single determination may lead to false impressions, and repeated tests may be necessary in order to arrive at a satisfactory decision. 3. A rapid rate is a warning signal that the renal lesion is active and progressing. 4. When the renal lesion is becoming quiescent the sedimentation

rate is less rapid, when the renal lesion is progressing the rate is more rapid. 5 The simplicity of the test is one of its best recommendations.

COMMENT

Acute nephritis is usually recognized when the attack is so severe that the renal function is for a time suppressed. This is followed by recovery, chronicity or death. Milder forms may pass unrecognized and untreated, and are frequently those which pass insidiously into the chronic form from which the patient rarely recovers. It is important to realize that the severest case of acute glomerular nephritis may heal promptly with no residual renal changes, while the mildest form may pass into the chronic. There seems to be a tendency to treat severe cases seriously, and to consider the acute case cured when the main syndromes have subsided. Owing to the fact that the immediate mortality in acute nephritis is low, many are led to view lightly the milder cases of acute nephritis and to be satisfied when the main symptoms of the acute stage have passed. We wish to emphasize that a mild infection of the type usually not considered important in the production of nephritis may be followed by an attack of acute diffuse nephritis so mild as to escape notice, and the signs and symptoms of this attack appear above the threshold of clinical recognition only after months or years have elapsed and the chronic stage has developed.

There is a pronounced lack of uniformity in the statistical reports of various authors concerning the etiology of acute diffuse glomerular nephritis. The disparity between the figures may be accounted for by the fact that some are compiled in hospitals for contagious diseases and others in children's hospitals, while still others are from general hospitals. If the urine were to be examined in all acute infections, both mild and severe, with the same care that it is examined in cases of scarlet fever, early and obscure cases of acute diffuse glomerular nephritis would more frequently be uncovered. As pointed out by Christian,¹⁸ the prevention of nephritis is extremely unsatisfactory, and all that can be done is to prevent as far as possible and treat as thoroughly as possible all acute infections, closely allied, he added, is the prophylaxis of the common cold and its sequelae. We have become more and more convinced, as we have advanced in this clinical study, that the neglected acute infection of the upper respiratory tract is an important cause of acute nephritis and that the mild acute case later becomes the average chronic case with no history of previous scarlet fever or of an acute phase.

If such poorly defined cases are to be diagnosed and treated in their incipency, then the usual textbook description of acute nephritis must

¹⁸ Christian, H. A. Types of Nephritis and Their Management, J. A. M. A. 102:169 (Jan 20) 1934.

be set aside to a large degree. That hypertension, hematuria and edema are the important features of acute glomerular nephritis is, of course, true, but this triad develops only in the patient who has suffered such a severe attack that for a time the kidneys are overwhelmed. In some well developed cases all the syndromes do not appear at the same time. Occasionally, the hypertension remains for a day and disappears, and edema may be so slight as to pass undetected, and hematuria may be present in the beginning and last for a few days, then disappear, or it may never occur at all.

Scarlet fever can no longer be looked on as the chief cause of glomerular nephritis, and the main clinical features cannot be embraced under hematuria, edema and hypertension, as was done formerly. When it is taken into consideration that ordinary colds in the head may be a cause of acute nephritis, and that symptoms may pass unrecognized during the entire course of the disease, many more cases of the acute phase will be diagnosed when sought for. It is apparent that the common cold is a term which has been applied to a variety of types of infections of the respiratory tract. A clear definition of the common cold is difficult to obtain, because various investigators hold different ideas concerning its essential nature. We have used the term in the sense in which it is used by the Thomsons¹⁹ in their monograph, "The Common Cold," in which they stated that the common cold is a generic term which covers a host of specific catarrhal infections of the mucous membrane of the respiratory tract. Concerning the term influenza, we found difficulty in differentiating between it and the common cold. The two terms are often used interchangeably, especially in periods during which no influenzal epidemic is present. In this series of cases the diagnosis of influenza was made when severe pains in the back and joints, headache and prostration dominated the clinical picture, and when the symptoms showed a tendency to be refractory to ordinary remedies. As pointed out by the Thomsons, although influenza and the common cold are very different diseases, the differential diagnosis is difficult, and no certainty in diagnosis will be forthcoming until definite causal organisms can be isolated with ease or until some scientific test has been developed. In grouping together these two etiologic factors in nephritis, we believe that we have avoided making a clinical separation in many cases, in which one practically does not exist.

Osman²⁰ said that it is wrong to consider scarlet fever as the most important cause of acute nephritis. He found that of fifty-six cases

19 Thomson, David, and Thomson, Robert. The Common Cold, Ann Pickett-Thomson Research Lab 8 1 (Dec.) 1932

20 Osman, A. A. Etiology and Prognosis of Acute Nephritis in Children and Young Adults. Clinical Study of 56 Cases, Guy's Hosp Rep 75 306 (July) 1925

of nephritis thirty-three, or 59 per cent, followed infections of the upper respiratory tract, three developed during pneumonia, two followed the puerperium, three developed after exposure to chills and fever, and in fifteen cases no reliable cause could be obtained. He also showed from the investigation of two hundred and thirty-five cases that scarlet fever had occurred in only eight. Scarlet fever was responsible in only four cases of thirty-four reported by Guild.²¹ Infections of the upper respiratory tract, such as the common cold and acute bronchitis, are the main causes in our experience. Other observers, including Boyd,²² Rake,²³ Lichtwitz,²⁴ Hill²⁵ and Longcope and his associates,² found that infections of the throat and upper respiratory passages far outstrip scarlet fever as a cause of acute nephritis. Fishbein,¹⁰ however, stated that scarlet fever is the most frequent cause of acute glomerular nephritis in children.

Evidence has been accumulating during recent years which tends to show that acute nephritis is one of the manifestations of late toxemia of pregnancy. Such an opinion has been expressed by Mussey and Keith,⁵ who reported that in forty-two cases of acute toxemia, clinical evidence of nephritis was present in all but five. Similarly, in a series of five hundred and forty-five consecutive deliveries of patients with toxemia excluding eclampsia and vomiting, Peckham and Stout²⁶ found that reexamination of 66.6 per cent of these months later revealed definite chronic nephritis in 40 per cent of those examined. In eclampsia, a characteristic glomerular lesion was described by Bell.⁶ An increase in the thickness of the capillary basement membrane and an increase of endothelial cells characterized the lesions. He concluded that the disease is a form of glomerular nephritis, but that it lacks some of the more striking features of acute glomerular nephritis, for instance, no epithelial crescents and no very large glomeruli are found. More recently, Band and Dunn⁷ studied the renal lesions in eclampsia and nephritis of pregnancy, and stated that the renal lesion closely simulates that of glomerulitis. In nine of ten cases of eclampsia they found the constant and predominant lesion to be in the glomeruli and to resemble that of acute glomerular nephritis.

21 Guild, H. G. Prognosis of Acute Glomerular Nephritis in Childhood, *Bull. Johns Hopkins Hosp.* **48** 193 (April) 1931.

22 Boyd, Gladys L. Acute Nephritis in Children, *Canad. M. A. J.* **17** 894 (Aug.) 1927.

23 Rake, G. W. The Role of Infections in the Etiology of Bright's Disease, *Guy's Hosp. Gaz.* **42** 242 (June 2) 1928.

24 Lichtwitz, L. *Praxis der Nierenkrankheiten*, Berlin, Julius Springer, 1925.

25 Hill, L. C. Febrile Albuminuria, with Special Reference to Pneumonia, *Quart. J. Med.* **22** 305 (Jan.) 1929.

26 Peckham, C. H., and Stout, M. L. Study of Late Effects of Toxemia of Pregnancy (Excluding Vomiting and Eclampsia), *Bull. Johns Hopkins Hosp.* **49** 225 (Oct.) 1931.

Although albuminuria is present in the urine of many patients with pneumonia, acute nephritis has been considered a rarity Hill,²⁵ who studied albuminuria of pneumonia rather fully, stated that of twenty-one cases of pneumonia of all types, five, or 23.8 per cent, were accompanied by evidence of renal disease sufficient to justify a diagnosis of nephritis. Blackman and Rake²⁷ reported that acute glomerular nephritis was found in 9.4 per cent of ninety-five cases of pneumococcal infections, however, no instance of acute glomerular nephritis was found in thirty-two cases of lobar pneumonia. In our series, eight cases, or 8.5 per cent, were traced to pneumonia. At times it is difficult to decide whether the urinary changes signify only febrile albuminuria or genuine but mild glomerular nephritis. In some cases, other evidence of nephritis, such as hypertension, may help make the decision, but as a rule we decided the question on the urinalyses. If red blood cells and granular casts were present in addition to the albuminuria, and these persisted for a week or more after the pneumonic process subsided, we diagnosed the case acute glomerular nephritis. The diagnosis in many cases must rest on the urinalysis, for other symptoms, as edema, hypertension and retention of nitrogen, are often lacking. Persistent albuminuria, with red blood cells, granular casts and pus cells, after the subsidence of an infection or disease capable of producing renal inflammation is taken for evidence of acute nephritis. More accurate studies of the urine by the quantitative method of Addis²⁸ are doubtless of great value in the diagnosis of the acute lesion, as well as in determining whether the lesion is becoming chronic or is healing. Our experience with this method has been too limited for discussion, but we believe from what we have done that it is a definite aid in prognosis.

Differences of opinion prevail concerning the incidence of hypertension during the acute stage. Christian and O'Hare²⁹ stated that of fifty-five cases, hypertension developed in nineteen. According to Bennett,³⁰ a moderate degree of hypertension is found in a small proportion of cases, and cases with a greater degree of hypertension are those in which chronic nephritis preexisted. Lichtwitz,²⁴ Volhard,¹ Volhard and Fahr³¹ and Kylin⁹ believed that hypertension is always

27 Blackman, S. S., and Rake, G. W. Acute Pneumococcal Nephritis, *Bull Johns Hopkins Hosp* **51** 217, 1932.

28 Addis, T. Haemorrhagic Bright's Disease. Natural History, *Bull Johns Hopkins Hosp* **49** 203 (Oct.) 1931.

29 Christian, H. A., and O'Hare, J. P. Nephritis, in Christian, H. A., and Mackenzie, J. *Oxford Medicine*, New York, Oxford University Press, 1920-1921, vol. 3, p. 674.

30 Bennett, T. I. Nephritis, Its Problems and Treatment, New York, Oxford University Press, 1929.

31 Volhard, F., and Fahr, T. *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

present during the acute stage. Others, as Fishbeig¹⁰ and Bennett,³⁰ expressed the belief that hypertension is more variable in its occurrence and apt to be absent at times. Our experience coincides with that of the latter group. One of our patients had no hypertension at the onset or during the course of the attack, and at autopsy typical acute diffuse glomerular nephritis was present. It is to be kept in mind, however, that hypertension may come and disappear in the early period of the acute phase before the reading of the blood pressure has been taken, furthermore, it may be absent at first and rise a few days later in the course of the disease. Kylin⁹ stated that, as a rule, an increase of blood pressure comes first, and that changes in the urine develop some days later. He cited a case in which high blood pressure, edema and uremia occurred in the absence of the urinary syndrome. In our series we found the urinary syndrome present in all cases, and no other syndrome was found to develop earlier than this.

It has been customary to think of uremia as the chief cause of the fatal issue in cases of acute nephritis. Levy,¹¹ however, called attention to the circulatory disturbances found in ten patients with acute diffuse glomerular nephritis. He believed that hypertension is the cause of the cardiac insufficiency. It is undoubtedly true that hypertension plays an important part in causing heart failure in many cases, but that other factors, such as the toxic action of uremia alone, may be the causative agent in some cases, as has been shown by the report of our case A.

The edema of acute nephritis is such a striking feature of many cases that formerly some writers spoke of certain cases of acute nephritis with edema as if this were a distinct type of nephritis. Furthermore, some believed that edema often is the first sign of acute nephritis, but in many instances it is only the first sign noticed, as the changes in the urine precede the formation of edema. Edema may be so slight as to pass unnoticed or it may last for only a few days and disappear entirely or again it may return at a later date during the transition into the chronic stage. When edema occurs, there may be a mere puffiness of the eyelids, occasionally it is more widespread, but general anasarca is rare. In view of the fact that the presence of capillary damage has been cited as a cause of edema in acute nephritis and that such damage has not been proved, Rennie³² attempted to determine whether any relationship exists between the degree of edema and the serum protein level in these cases. Of sixty-three cases in his series, nine, or 14 per cent, had low serum protein levels (below the edema-producing level). In these cases edema occurred, and he attributed it to a decrease in plasma protein. In other cases, the plasma protein levels were only slightly reduced, and edema also occurred. Rennie believed that in the latter a rise in the blood pressure plus the drop

32 Rennie, J. B. Oedema in Nephritis, *Quart J Med* 2:521 (Oct.) 1933

in the plasma protein level are jointly accountable for the edema. In a few cases in which no reduction of plasma protein was present a sharp rise in the blood pressure was, in Rennie's opinion, the main factor in causing the edema. Peters and Van Slyke³³ said that throughout the acute attack the plasma protein level may be unaffected, provided the attack is mild, otherwise there may be a decided fall in the protein level within a month. It must be taken into consideration, however, that in the earliest stages of acute nephritis, edema may dominate the clinical picture before any change occurs in the plasma protein osmotic pressure. They attributed this early edema not to a loss of protein osmotic pressure in the plasma, but to some quite different physical cause, presumably an increase in capillary permeability.

In our experience with this problem we have found slight or no reduction in the quality of plasma protein in the initial stage of the acute attack, when edema usually occurs. In the cases becoming sub-acute and chronic there was a tendency for the plasma protein level to fall. This reduction was pronounced in only a few cases and never as severe as that seen in lipoid nephrosis and chronic nephritis. In the cases which went on to the chronic stage, a fall in the plasma protein level was more commonly observed, and the determination of this decrease is one of the reliable prognostic guides. When edema developed during the latter periods of the acute stage in the patient whose condition went on to a chronic phase, a fall in the plasma protein to the edema-forming level was occasionally seen.

The term acute focal nonembolic glomerular nephritis is used by some, in contrast to acute diffuse glomerular nephritis, to designate cases characterized chiefly by albuminuria and the predominance of red blood cells in the urine. The absence of other features, like edema, hypertension and retention of nitrogen, is essential for this diagnosis. We believe that the clinical differentiation between genuine acute diffuse glomerular nephritis and the acute nonembolic focal type is difficult to make. We have seen the necessary symptoms on which to base a diagnosis of focal nephritis in cases which proved later to be genuine diffuse glomerular nephritis. Some observers look on cases of mild acute nephritis as a form of the focal type. Such mistakes in diagnosis frequently result in the lack of proper safeguards for the patient, whose ultimate fate is renal failure from a slow but progressive form of diffuse glomerular nephritis. Our observations have led us to believe that it is better to avoid making this clinical distinction in many cases in which practically none exists and to consider them as representative of a stage of diffuse nephritis rather than a distinct type.

³³ Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932.

With reference to the sedimentation rate of erythrocytes as a prognostic guide in nephritis, Kollert³⁴ found it of some help in determining whether or not the lesion of chronic glomerular nephritis was active or healing. In a critical analysis of the sedimentation test in its application to gynecology and obstetrics, surgery and general medicine, Walton³⁵ found that its most important use was that of a prognostic agent. In dealing with acute nephritis his case 143 was of particular interest to us. The patient was admitted to the hospital suffering from an attack of acute nephritis incidental to acute tonsillitis. A rapid sedimentation rate was found, but a month later, when all fever had subsided and albuminuria had ceased, another sedimentation test revealed a normal figure. In this case the nephritis cleared up promptly, if it had not cleared up, the sedimentation test perhaps would have remained rapid. The rapid sedimentation rates in many of our cases of acute nephritis were independent of the febrile stage of the causal disorder.

It is supposed by some, as pointed out by Aldrich and Boyle,³⁶ that there are cases of chronic glomerular nephritis which develop slowly and insidiously without having the initial acute stage. Perhaps a certain portion of such cases were in the unrecognized class during the mild acute onset, and passed unobserved into the chronic form. Such cases frequently illustrate that mild acute glomerular nephritis may develop and pass unrecognized through the transitional stage into the chronic form in a person who is oblivious of the fact that anything abnormal has occurred in the kidneys. We are aware that there is no measuring rod with which to determine accurately the degree and extent of the activity of the nephritic lesion in the stage of transition or in the early chronic phase. But if the simple methods outlined here are employed, it is possible that a better understanding of the true course of the disease may be obtained, resulting in an effort to prevent the onset of chronic glomerular nephritis by providing for the patient the proper safeguards which are often neglected.

SUMMARY

1. In ninety-four cases of acute diffuse glomerular nephritis the clinical features have been described, and essential data have been summarized in tables. Detailed information is given in tables 7 and 8 of twenty cases which became chronic and of ten selected cases in which recovery was made. The age incidence in relation to outcome, the

34 Kollert, V. Nephritis, *Aerztl Praxis* 6:1 (Jan 15) 1932.

35 Walton, A. C. R. The Erythrocyte Sedimentation Test, A Clinical and Experimental Study, *Quart J Med* 2:79 (Jan) 1933.

36 Aldrich, C. A., and Boyle, H. H. Chronic Nonspecific Nephritis. Clinical Observations on 40 Children with Results of Treatment on Full Diets, *J. A. M. A.* 100:1979 (June 24) 1933.

causes of death in twenty-seven cases, the etiologic agents and the chief clinical syndromes have been analyzed clinically

2 Acute diffuse glomerular nephritis may result from mild forms of infection of the upper respiratory tract, not usually considered as causal factors in acute nephritis

3 The acute phase of glomerular nephritis may be so mild that it passes unrecognized, and no indication of renal damage is observed until the disease has progressed into the chronic stage, when renal insufficiency sets in

4 There is a period in the course of the disease, coming after the early symptoms of the acute phase have subsided, that is called the stage of transition, in which the patient is frequently considered cured, but in reality the renal lesion continues to be unhealed, and progresses toward the chronic stage unrecognized and untreated

5 It has been shown that if the cases in this period are studied with the aid of the several simple methods given here, the true course of the disease may be determined. Special attention has been paid to the blood urea clearance test and the erythrocyte sedimentation rate in determining whether the renal lesion has completely healed or has become quiescent temporarily, only to become active later on

6 A study of cases in the stage of transition is of utmost importance, because if the true condition is recognized at this time the proper safeguards may be provided which perhaps will interrupt the progress of the renal inflammation before chronic glomerular nephritis has come to full fruition

EFFECT OF CARDIAC INFARCTION ON THE TOLERANCE OF DOGS TO DIGITALIS

AN EXPERIMENTAL STUDY

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The literature concerning the tolerance to digitalis in clinical cases of coronary occlusion is meager. The few reports with which we are acquainted consist chiefly of clinical impressions. Moreover, the conclusions of various observers are not entirely in agreement. Herrick¹ stressed the great value of digitalis in coronary occlusion and suggested that rapid effects be sought in some cases by intravenous or intramuscular injection. Riesman² felt that digitalis should not be used in coronary occlusion, believing that because of its great damage to the myocardium it would do no good and might do harm. Bastedo³ stated that in cases of coronary sclerosis and myocarditis, regardless of rhythm, digitalis must be used with care and never in massive doses.

Conclusions based on experiments with animals likewise are somewhat at variance. Gold⁴ reported in 1925 that there was no significant variation in the tolerance of cats to ouabain after coronary occlusion as compared to those in a control group. He concluded that "the experimental evidence lends no support to the fear that in coronary occlusion digitalis may precipitate ventricular fibrillation more readily than in the normal heart." Gilbert and Fenn⁵ obtained a decrease in the coronary flow in dogs treated with digitalis which they believed was due to vaso-

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1 Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* **69** 2015 (June 22) 1912.

2 Riesman, D. Coronary Thrombosis, *M. Clin. North America* **6** 851, 1923.

3 Bastedo, W. A. The Present Status of Digitalis Therapy, *Ann. Clin. Med.* **5** 993, 1927.

4 Gold, H. Action of Digitalis in the Presence of Coronary Obstruction, *Arch. Int. Med.* **35** 482 (April) 1925.

5 Gilbert, N. C., and Fenn, G. K. Effect of Digitalis on the Coronary Flow, *Arch. Int. Med.* **50** 668 (Nov.) 1932.

constriction. They stated that a great deal of caution should be used in the administration of digitalis in the presence of coronary disease.

Because of the widespread tendency to use digitalis in the presence of any severe cardiac weakness, tolerance of the recently infarcted heart to digitalis and the wisdom of using this drug in large doses under these conditions would seem to be important.

Since the matter is a difficult one to settle by clinical observation alone, we attempted to study the matter further by experiments, realizing at the same time the limitations that stand in the way of applying such results directly to human medicine.

METHOD

Dogs weighing from 7.6 to 15.0 Kg. were used for our experiments. The anterior descending branch of the left coronary artery and, in some cases, the accompanying vein were ligated in continuity, as described in a previous report,⁶ in order to produce occlusion and subsequent infarction. After varying periods of time (from thirty minutes to six months) the tolerance of the animal to digitalis was determined by a method similar to that described by Burn⁷ for the assay of digitalis on cats. Freshly prepared tincture of digitalis diluted twenty times with physiologic solution of sodium chloride was given by continuous infusion into the femoral vein at a rate of 0.025 cc. per kilogram of body weight per minute. By using a tincture of about standard strength, this rate of administration was sufficient to cause death in normal dogs in from thirty to forty-five minutes. Light ether anesthesia and artificial respiration were used on all animals except in four of the control experiments on normal animals. Blood pressure of the carotid was recorded graphically during administration of the drug. At the conclusion of the experiment the heart was carefully removed and examined for pathologic changes. Usually an area of infarction involving the apex, anterior wall and a portion of the lateral wall of the left ventricle was seen.

RESULTS

Table 1 shows the results obtained in the assay of the tincture on normal dogs. Two tinctures varying slightly in strength were used. With tincture A, the lethal dose ranged from 0.8 to 0.94 cc. per kilogram in four experiments in which artificial respiration was not used, the average being 0.85 cc. per kilogram. In two dogs on which artificial respiration was used the average lethal dose was 0.90 cc. per kilogram. With tincture B, the lethal dose varied from 0.84 to 1.16 in seven dogs and averaged 1.02 cc. per kilogram. Artificial respiration was used on all these animals. From these data it was concluded that the lethal dose in dogs by the method used gave figures which varied

6 Bellet, S., and Johnston, C. G. The Effect of Coronary Occlusion Upon the Initial Phase of the Ventricular Complex in Direct Chest Leads. An Experimental Study, *J. Clin. Investigation* **13** 725, 1934.

7 Burn, J. H. *Method of Biologic Assay*, New York, Oxford University Press, 1928.

within a fairly small range⁸ The values obtained from the lethal dose were apparently slightly higher when artificial respiration was used In some of the dogs under artificial respiration a sudden drop in pressure almost to zero was noted from two to three minutes before death This pressure gradually rose again and continued for a brief period before finally dropping to zero This preagonal drop might have been considered the end-point in these dogs if artificial respiration had not been used

TABLE 1—*Standardization of Normal Dogs*

Date of Standardization	Dog	Weight, Kg	Tincture A Lethal Dose, Cc per Kg	Tincture B Lethal Dose, Cc per Kg	Time of Infusion, Min
4/13/33	878	13.8	0.80		33.0
4/13/33	881	12.8	0.94		38.0
4/18/33	885	12.7	0.82		33.5
4/20/33	892	12.0	0.85		34.0
5/30/33	1,025	15.0	0.92		37.0
5/30/33	1,029	12.5	0.88		35.5
6/20/33	1,043	13.3		1.13	46.0
6/20/33	1,024	12.0		1.15	45.0
7/ 8/33	6	11.9		1.16	46.0
7/ 8/33	7	14.0		0.94	37.5
7/13/33	8	15.8		0.86	34.5
7/13/33	9	11.2		0.84	33.5
7/13/33	10	13.9		1.05	42.0

TABLE 2—*Standardization Four Days After Operation, No Infarction Present (Control Animals)*

Date of Standardization	Dog	Weight, Kg	Tincture A Lethal Dose, Cc per Kg	Tincture B Lethal Dose, Cc per Kg	Time of Infusion, Min
4/27/33	891	7.8	0.85		33.0
5/ 6/33	910	9.0	0.89		37.0
5/ 6/33	911	7.6	0.85		34.0
6/18/33	960	7.9		1.28	51.5

Table 2 shows the values obtained in the animals to which digitalis was administered four days after operation without coronary occlusion They were subjected to the same operative procedure as the animals in which cardiac infarction was produced except that the coronary artery was not tied They therefore served as excellent controls in our study of the effect of the operative procedure on the tolerance to digitalis The values obtained with tincture A ranged from 0.85 to 0.89 cc per kilogram With tincture B the value was 1.28 cc per kilogram in one dog These values were practically identical with the normal values obtained for these animals with the respective tinctures, and they indi-

⁸ Ten dogs were standardized with a third tincture for another type of experiment The lethal dose varied from 0.96 to 1.15 cc per kilogram, the maximum variation being about 10 per cent above or below the average By the method used, the figures for standardization in the dog varied within a much narrower range than those in the cats

cated that the operative procedure per se had no effect on the tolerance of the animals to digitalis four days after operation

Table 3 shows the figures obtained in the experiments in which the tolerance was determined from thirty to forty minutes after ligation of the coronary artery. In three of these dogs the values ranged from 0.85 to 0.89 cc per kilogram, practically the same as those obtained in the normal animals. In the remaining two of the five animals the values were even slightly higher than those obtained in normal animals. The probable cause and significance of the latter values will be discussed later. It may be said, however, that there was no evidence of a decrease

TABLE 3—*Standardization One-Half Hour After Ligation of Anterior Descending Branch of Left Coronary Artery and Vein*

Date of Standardization	Dog	Weight, Kg	Tincture A Lethal Dose, Cc per Kg	Time of Infusion, Min
4/29/33	903	12.0	0.85	54.0
4/29/33	904	14.8	0.89	38.0
5/2/33	912	13.0	0.89	35.5
4/22/33	894	12.0	1.00	41.0
5/22/33	997	13.2	1.03	41.3

TABLE 4—*Dogs Standardized Four Days After Coronary Ligation, All Showing Cardiac Infarction*

Date of Operation	Date of Standardization	Dog	Weight, kg	Tincture A Lethal Dose, Cc per Kg	Tincture B Lethal Dose, Cc per Kg	Time of Infusion, Min	Comment
4/14/33	4/18/33	879	16.0	0.70		28.0	Large infarction
4/26/33	4/29/33	858	11.7	0.65		26.5	Large infarction
5/18/33	5/23/33	985	8.7	0.69		28.0	Large infarction
5/20/33	5/24/33	991	14.5	0.63		25.0	Very large infarction
6/14/33	6/18/33	993	7.8		0.77	31.0	Large infarction
6/19/33	6/23/33	932	15.0		0.77	31.0	Medium infarction
6/21/33	6/25/33	1,052	15.0		0.85	34.0	Small infarction

in tolerance in digitalis from thirty to forty minutes after ligation of the coronary arteries

Table 4 shows the results obtained when digitalis was administered to dogs on the fourth day after ligation of the coronary artery. These dogs had definite infarction of the muscle of the heart which varied somewhat in extent in the different animals. With tincture A the values in four dogs ranged from 0.63 to 0.70 cc per kilogram. With tincture B the figures for the lethal dose in three dogs were 0.77, 0.77 and 0.85 cc per kilogram, respectively. The area of infarction in the last dog was quite small, its extent being less than that in any of the others of this group. The average lethal dose was 0.8 cc per kilogram, as compared to 1.02 cc in the normal dogs.

These figures were definitely below the range of values obtained in the normal dogs. Except for one animal (dog 1052) which received

tincture B and in which the infarction was small, the tolerance of the animals with the acute infarction was below even the lowest figures of the animals in the normal control groups. The decrease in tolerance ranged from about 20 to 30 per cent below the average for the normal controls. In spite of the presence of cardiac damage the animals appeared to be in fair condition before the final assay. In general, the dogs showing the largest infarction exhibited the poorest tolerance to digitalis.

Table 5 shows the values obtained in four dogs in which ligation of the coronary artery was performed from six weeks to six months before assay. These animals had infarctions involving the apex and the lower portion of the anterior wall of the left ventricle. During the chronic stage the extent of infarction was considerably less than in the acute stage. These animals were studied electrocardiographically during this period, and tracings taken in the latter part of this period

TABLE 5—*Standardization in Chronic Infarction*

Date of Operation	Date of Standardization	Dog	Weight, Kg	Lethal Dose Tincture A, Cc per Kg	Lethal Dose Tincture B, Cc per Kg	Time of Infusion, Min
10/20/32	5/ 4/33	328	11.8	0.75		29.5
10/21/32	5/ 4/33	261	13.0	0.75		30.0
5/30/33	7/15/33	803	15.6		0.79	32.3
5/30/33	7/15/33	959	9.0		1.00	40.0

showed a considerable return to normal, indicating that healing had taken place. The lethal dose for these animals was 0.75 cc per kilogram with tincture A. In two dogs standardized with tincture B six weeks after ligation of the coronary artery the lethal dose was 0.79 and 1 cc per kilogram, respectively. Both animals showed an area of chronic infarction about 2 cm in diameter involving the anterior wall of the left ventricle near the apex. In three of the four animals with chronic infarction the lethal dose was below that required for the normal, and the values obtained ranged approximately between those obtained for the animals with acute infarction and those for the normal controls. In one dog the lethal dose was within the normal range.

COMMENT

Choice of the experimental animal is not an unimportant matter. In our early experiments we used the cat, as did Gold⁴ in somewhat comparable experiments. We discarded this animal for the dog for two reasons. First, the end-point in the cat, as determined by the fall in blood pressure to zero, was often gradual and not rapid. Second, cats

withstand ligation of the coronary artery quite well,⁹ and are often resistant to the inception of ventricular fibrillation. We were able to ligate both coronary arteries in some of these animals without ventricular fibrillation occurring. Moreover, in the instances in which ligation of isolated coronary arteries produced ventricular fibrillation, this arrhythmia not infrequently reverted spontaneously to a normal rhythm. We never observed this in the dog, although rare instances of recovery from ventricular fibrillation under these conditions have been reported.¹⁰

There appears to be a sound physiologic reason why the heart of the cat is more refractory to the development of ventricular fibrillation than that of the dog. McWilliam^{9a} noted that spontaneous recovery from ventricular fibrillation took place readily in the heart of the cat, rabbit, mouse, hedgehog and fowl in contrast to the hearts of larger animals. He found that the large beef heart, for example, entered into the fibrillary state with the greatest ease and caprice. Garrey^{9b} demonstrated that the ease with which the fibrillary process may be induced, and with which spontaneous recovery from the fibrillary contractions takes place is, in general, inversely proportional to the mass of fibrillary tissue.

In view of these considerations, we discontinued the use of the cat in favor of the dog after a few preliminary experiments¹¹ because we felt that the effects of ligation of the coronary artery in the larger heart of the dog were more comparable to those observed in the human heart. Dogs proved quite satisfactory for these experiments. By the method used they were standardized with a fair degree of accuracy and the end-point, as denoted by a sudden drop in blood pressure in practically all cases, was definite and clearcut.

RELATIONSHIP BETWEEN THE STAGE OF INFARCTION AND THE TOLERANCE TO DIGITALIS

Ligation of a coronary artery sets off a series of events in the muscle involved that lasts for a variable period of time (from four to six weeks) until the chronic stage is reached. First, there are inaugurated the processes that lead to death and necrosis, which may not reach their maximum development for several days after coronary

9 (a) McWilliam, A. Fibrillar Contraction of the Heart, *J. Physiol.* **8** 296, 1887. (b) Garrey, W. E. The Nature of Fibrillary Contraction of the Heart. Its Relation to Tissue Mass and Form, *Am. J. Physiol.* **33** 397, 1914.

10 Porter, W. T. The Recovery from Fibrillary Contractions, *Am. J. Physiol.* **1** 71, 1898.

11 In our initial experiments with cats no definite diminution in tolerance to digitalis was noted, even with definite myocardial infarction from six to eleven days after ligation of the coronary artery. In these instances the end-point was not clearcut, and the fall in blood pressure was gradual and was maintained over a relatively long period.

occlusion These are followed by the slower processes of healing At varying stages in this somewhat protracted process, the histologic condition of the muscle varies greatly

In the chronic stage, for example, six weeks or more after ligation of the coronary artery, the muscle is demonstrably abnormal only to the extent of having a scar, all evidences of inflammation and necrosis having been removed In contrast, in the acute or subacute stage, a few days after ligation, the involved myocardium shows inflammation, edema and necrosis, and the muscle is thick, boardlike and probably noncontractile

In a still earlier stage, from a few minutes to one-half hour after ligation, in spite of the presence of currents of injury as revealed by the electrocardiograph, no histologic evidences of infarction are present For some time after occlusion, the changes in the muscle are probably reversible, i e., if circulation can be restored, the muscle will return to normal We saw this occur in two dogs when a ligature, applied tightly enough to produce typical electrocardiographic effects, and known to have been effective for at least fifteen minutes, subsequently slipped and permitted the muscle to be entirely restored to normal, so far as histologic and electrocardiographic studies revealed

Between this stage and that of maximum necrosis, the changes undergone by the muscle are great and more or less progressive Just when the stage of maximum necrosis is reached we do not know, but we suspect that from twenty-four to forty-eight hours at least are required for its full development We suspect this not only because of the histologic observations made on the hearts used in these experiments, but because of electrocardiographic studies of coronary occlusion in hearts of both dog and man It is a common experience to find that the curves obtained by semi-direct leads of the chest do not reveal their maximum change for twenty-four hours, or even longer, after occlusion has taken place⁶

Feeling that the tolerance to digitalis after coronary occlusion might be directly related to and depend on the degree of pathologic change in the involved muscle, we made our determinations during three stages of this complicated process one-half hour after ligation, from three to four days after occlusion and in the period of from six weeks to six months after the original ligation

As we have already pointed out, our results indicated a rather striking diminution of tolerance in the stage of maximum necrosis, a slightly diminished tolerance in the chronic or healed stage and a normal tolerance in the period of from thirty to forty minutes after closure of the coronary artery Moreover, the degree of diminished tolerance noted during the stage of necrosis appeared to be proportional to the size of the necrotic area That the operation itself had no effect on the tolerance to digitalis was shown by the results obtained in the animals

which had been subjected to exactly the same operative procedure as those with myocardial infarction, with the exception that the coronary arteries were not ligated. The tolerance of these animals to digitalis was within normal limits (table 3).

These results point to conclusions that are different from those drawn by Gold⁴ from somewhat comparable experimental work. His method, however, differed from ours in two important respects. First, he used cats which, as we have already pointed out, appear to withstand ligation of the coronary artery particularly well. Second, his determinations of tolerance were made at a relatively early stage in the process of infarction, from forty minutes to twenty-four hours after ligation.

Because of physiologic reasons already cited, we feel that results obtained in dogs are more apt to be applicable to man than those obtained in smaller animals. Therefore, we believe that our conclusions have certain implications, at least in the human problem. We are more willing to give them weight in this connection because they coincide with our clinical impressions, which lean strongly to the view that the more damaged the heart is, the less is its tolerance to digitalis.

SUMMARY

The tolerance of dogs to digitalis was determined at various intervals of time after ligation of the coronary artery: one-half hour after ligation of the coronary artery, four days later (during the stage of acute and subacute infarction) and from six weeks to six months later (during the stage of chronic infarction). The tolerance of these animals was compared with that of animals in a normal control series.

Dogs standardized within one-half hour after ligation showed no diminution in tolerance to digitalis as compared with those in a control group. During the stage from acute to subacute infarction there was a diminished tolerance to digitalis which averaged from about 20 to 30 per cent below the average of the figures for the normal controls.

In the animals with chronic infarction, in which the area of infarction was considerably smaller than in the acute or subacute stage (standardized from six weeks to six months after ligation of the coronary artery), the tolerance was less than that of the normal animals but higher than that of the group with the subacute infarctions.

The diminution in tolerance after ligation of the coronary artery apparently depends on the presence of infarction and probably also on the extent and stage of the infarcted area. These findings lend support to the clinical impression that digitalis in massive doses may be dangerous during the stage of subacute and chronic infarction, and that it should be used with caution in such cases.

Dr. A. N. Richards placed the facilities of his laboratory at the disposal of the authors, and Dr. C. F. Schmidt furnished valuable advice.

RELATIONSHIP BETWEEN OXYGEN CONSUMPTION AND NITROGEN METABOLISM

IV EXPERIMENTS ON ANIMALS

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Variations in the rate of oxygen consumption are met with in numerous conditions in which no disturbance in thyroid function has been recognized. Prominent among such conditions are the hematopoietic diseases. In a series of investigations I have attempted to evaluate some of the abnormal physiologic processes in the blood dyscrasias in terms of their effect on the oxidative processes of the organisms as a whole. Studies have been made on patients with pernicious anemia, leukemia and polycythemia vera, as well as on dogs with acute hemorrhagic anemia, hemolytic anemia, induced polycythemia and phlorhizin diabetes.

The previous communications concerning pernicious anemia, leukemia and polycythemia vera will be briefly summarized. The reader is referred to the original publications for details and bibliographies.

STUDIES ON MAN

Pernicious Anemia—The object of the studies of pernicious anemia, which were carried out by my associates and me was to determine the effect of rapid erythropoiesis on the total oxygen consumption. Ten patients with severe pernicious anemia were studied, and part of the data have been published¹. The pertinent information derived from these studies may be summarized as follows:

1. In eight of the ten patients the total oxygen consumption decreased during the period of most rapid erythropoiesis. In the other two patients there was no significant change in the gaseous metabolism. In the eight cases the total decrease in basal metabolic rate varied from 50 to 15 per cent. In patients who were without fever and for whom the control periods were sufficiently long the decrease was found to be between 15 and 20 per cent. This drop occurred regardless of whether the control level was above or below the calculated normal.

From the Department of Physiology, University of Chicago

1. Baldrige, C W, and Barer, A. Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism. I. In Pernicious Anemia, J Clin Investigation 10: 529, 1931.

2 During the period of rapid erythropoiesis and decreased oxygen consumption there was moderate storage of nitrogen in all of the four cases in which nitrogen balances were determined

3 One large dose of liver extract per week by mouth caused the same gradual decrease in oxygen consumption which occurred with smaller daily doses

4 In nearly every instance the total oxygen consumption gradually decreased throughout the reticulocytic crisis

5 It is obvious that the formation of blood greatly exceeded the destruction of blood during the period of decreasing oxygen consumption

Leukemia—Chronic leukemia under treatment by irradiation affords a circumstance in which the destruction of blood temporarily exceeds the formation of blood. Nine patients with chronic leukemia were studied before and after irradiation, and the data have been published.² The reader is referred to this publication for details of the metabolic studies and for a discussion of the existing theories as to the cause of the increased gaseous metabolism in leukemia.

The results of our investigations on leukemic patients may be summarized as follows:

Following a large dose of roentgen irradiation there is an abrupt increase in the excretion of nitrogen. The nitrogen balance becomes negative, owing to decreased ingestion and increased endogenous nitrogen catabolism. The total oxygen consumption increases within six hours after irradiation, and the increase may last for four days or may disappear within twenty-four hours. The magnitude and duration of the increase in gaseous metabolism seem to depend on the degree and duration of protein catabolism occasioned by the irradiation.

After the preliminary increase in the excretion of nitrogen which follows irradiation, the urinary nitrogen gradually decreases, often to a level below that of the control period. During this period of lowered catabolism of protein the nitrogen balance becomes positive, and the gaseous metabolism decreases.

Polycythemia Vera—In polycythemia vera, the destruction of blood can be made to exceed the formation of blood by the administration of phenylhydrazine. Two patients with polycythemia vera were studied during intoxication by phenylhydrazine, and the data have been reported.³

2 Baldrige, C. W., and Barer, A. Relationship Between Oxygen Consumption and Nitrogen Metabolism. II. In Leukemia, *Arch Int Med* **51** 589 (April) 1933.

3 Barer, A., Paul, W. D., and Baldrige, C. W. Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism. III. In Polycythemia Vera, *J Clin Investigation* **13** 15 (Jan) 1934.

The results of our studies of leukemia and polycythemia vera were quite similar so far as the relationship between nitrogen catabolism and oxygen consumption was concerned. Phenylhydrazine produced a marked decrease in the number of erythrocytes, a negative nitrogen balance, due largely to the increased catabolism of protein, and an increase in the basal metabolic rate. No attempt has as yet been made to establish a quantitative relationship between the loss of endogenous nitrogen and the increase in oxygen consumption by the body, but the destruction of nonnucleated erythrocytes by phenylhydrazine seems to require about as much oxygen per gram of nitrogen as does the destruction of nucleated leukemic cells by irradiation.

ADDITIONAL STUDIES ON ANIMALS

The oxygen consumption of the dogs was measured by the Benedict closed circuit apparatus with attachments described by Kunde.⁴ Four well trained dogs were used. Before control periods were begun, tests were made daily for periods of ten, thirteen and twenty-eight days, respectively, on three previously trained dogs. Dog 4 had not previously been trained, so that a control period was not begun until the oxygen consumption was fairly constant and the average for several days was below the calculated normal consumption. Tests were made at about the same time each day, at least twenty hours after food was taken and after a preliminary period of rest of at least twenty minutes. The tests were run for twenty minutes, and calculations were based on the last fifteen minutes of this period. Determinations were made daily without exception over a period of about eight months. On a few occasions when extraneous influences of one kind or another caused the dogs to move, the tests were repeated. Seven times the second test was unsatisfactory, and though it was recorded, it was not used in the calculations of averages. Two other determinations were unsatisfactory because the dogs obtained food by mistake. Thus, of a total of eight hundred determinations, nine were considered to be unsatisfactory. One dog suffered a short febrile illness after bleeding, which invalidated the results of one experiment (dog 3, chart 4).

According to the work of Kunde and Steinhaus,⁵ the average basal metabolism of normal dogs is 7712 calories per square meter each twenty-four hours. This figure has been used as the normal, and the surface area has been calculated from Meeh's formula.⁵ As no attempt has been made to compare the metabolism of one animal with that of another, there is no need to discuss the shortcomings of the Meeh formula for the determination of the surface area of the dog. All of the temperatures were taken rectally.

Hemorrhagic anemia was produced by bleeding the dogs with a needle from the jugular or femoral veins. About 25 cc of blood per kilogram of body weight was removed on each of two successive days. The blood was removed just after the determination of the basal metabolic rate on the day indicated.

Transfusions were done by the indirect method, the blood being given by means of gravity. Fifty cubic centimeters of 2.5 per cent sodium citrate solution was used

4 Kunde, M. M. The After Effects of Prolonged Fasting on the Basal Metabolic Rate, *J. Metab. Research* 3: 399, 1923.

5 Kunde, M. M., and Steinhaus, A. H. Studies on Metabolism. IV. The Basal Metabolic Rate of Normal Dogs, *Am. J. Physiol.* 78: 127 (Sept.) 1926.

as an anticoagulant for each transfusion. About 50 cc of whole blood per kilogram of body weight was given in experiments 5, 6 and 7. In experiment 8B, dog 1 died the day after receiving 375 cc of whole blood. The blood given in experiments 5, 6 and 7 was found to be compatible by cross-matching. The blood given to dog 1 in experiment 8B was from the donor that had been used in the three transfusions for dog 1 in experiment 5, but cross-matching was not done before the last and fatal transfusion.

The citrated plasma which was given intravenously in experiments 8A and 9B was obtained from the donors from which these recipients had previously received transfusions of whole blood. In each instance the whole blood had been diluted with 50 cc of 25 per cent sodium citrate, and the citrated plasma obtained by centrifugation.

In experiments 9A, 10A and B and 11A the corpuscles and plasma were separated by centrifugation, and the corpuscles were hemolyzed by the addition of distilled water.

The charts for the experiments with phlorhizin are almost self-explanatory. One gram of phlorhizin was given in each instance. Merck's phlorhizin was recrystallized from alcohol as suggested by Lusk⁶. The recrystallized phlorhizin was dried and suspended in sterile olive oil for subcutaneous injection. The loss of nitrogen through the feces and hair was not determined in these animals.

The diets were as follows:

Dogs 1 and 2, from June 22 to July 13, 1931, were given 250 Gm of chopped beef lung, 225 Gm of bread, 250 cc of milk and about 20 Gm of bone meal daily in one feeding. From July 14 to October 9, 200 Gm of chopped beef lung was given, the other constituents were unchanged. From October 10 until the death of dog 1 on December 2 and until the beginning of the phlorhizin experiment in dog 2 on December 17, the chopped beef lung was reduced to 150 Gm daily, with no other change in the diet.

Dog 3 was given chopped beef lung as follows: from June 22 to July 13, 1931, 300 Gm daily; from July 14 to October 9, 250 Gm daily and from October 10 to Jan 9, 1932, 200 Gm daily. The amounts of bread (225 Gm), milk (250 cc) and bone meal (about 20 Gm) remained constant from June 22, 1931, to Jan 9, 1932.

Dog 4 was obtained on July 21, 1931, his diet corresponded with that of dogs 1 and 2 until the beginning of the experiment with phlorhizin on December 24.

Liver extract, when given, was given in addition to the regular diet. Liver extract with iron (equivalent to 300 Gm of whole liver) was given daily for twenty days to each of the dogs that were bled. In dog 3 it was begun immediately after bleeding while in dogs 1 and 2 it was started ten days after bleeding.

Several determinations were made in addition to the metabolic studies. The weight, pulse rate, respiratory rate, temperature, hemoglobin (Sahli), hematocrit value and erythrocyte and leukocyte counts were determined daily. For these determinations 1 cc of blood was withdrawn from a vein and added to a few small crystals of neutral potassium oxalate. Care was taken to prevent settling of the corpuscles.

RESULTS

Acute Hemorrhagic Anemia—After control periods of twelve, twelve and fifteen days, respectively, dogs 1, 2 and 3 were bled about

⁶ Lusk, G. The Science of Nutrition, Philadelphia, W. B. Saunders Company, 1928, p. 626.

25 cc per kilogram of body weight on each of two successive days (charts 1, 2, 3 and 4) The dogs had been in the laboratory for many months and had been on an adequate diet, so that the blood counts of the controls were higher than the average for recently impounded dogs After bleeding there was a gradual restitution of hemoglobin and erythrocytes in each instance The previous normal level was reached in about twenty days, while at the end of thirty days after bleeding

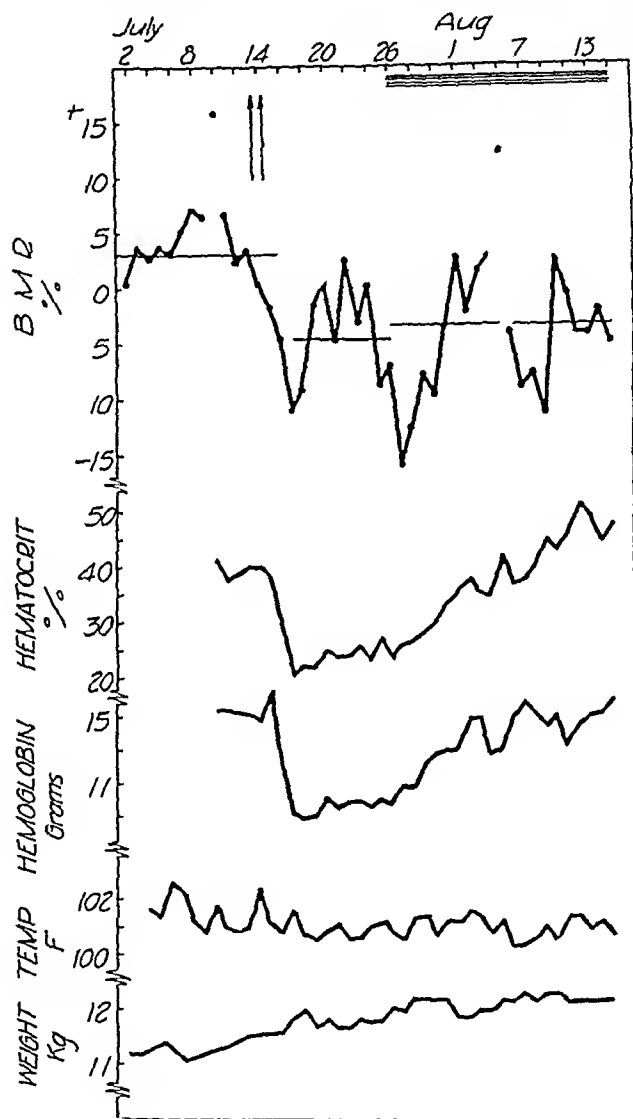


Chart 1 (dog 1) —Two hundred and seventy cubic centimeters of blood was drawn on July 13, and 270 cc on July 14, 1931, as indicated by the arrows The dog weighed 11.5 Kg, and the blood volume of all of the dogs was estimated to be 100 cc per kilogram of body weight The control period was twelve days, but on one day the metabolism test was unsatisfactory Liver extract with iron (equivalent to 300 Gm of whole liver per day) was given for twenty days beginning ten days after bleeding, as indicated by the parallel lines in the upper right hand corner Here, as in all of the subsequent charts, the control average and the averages for ten-day periods during the experiment are indicated by horizontal lines through the curve of the basal metabolic rate

there was a distinct and permanent overcorrection in the hemoglobin and the number of erythrocytes. During the first ten days of this period of rapid formation of blood the average oxygen consumption was found to be 71, 79 and 93 per cent, respectively, below the control averages. The basal metabolic rates continued low throughout the entire period of blood regeneration, during which all of the dogs gained in weight (0.4, 1 and 1.2 Kg, respectively). Nitrogen balances were not deter-

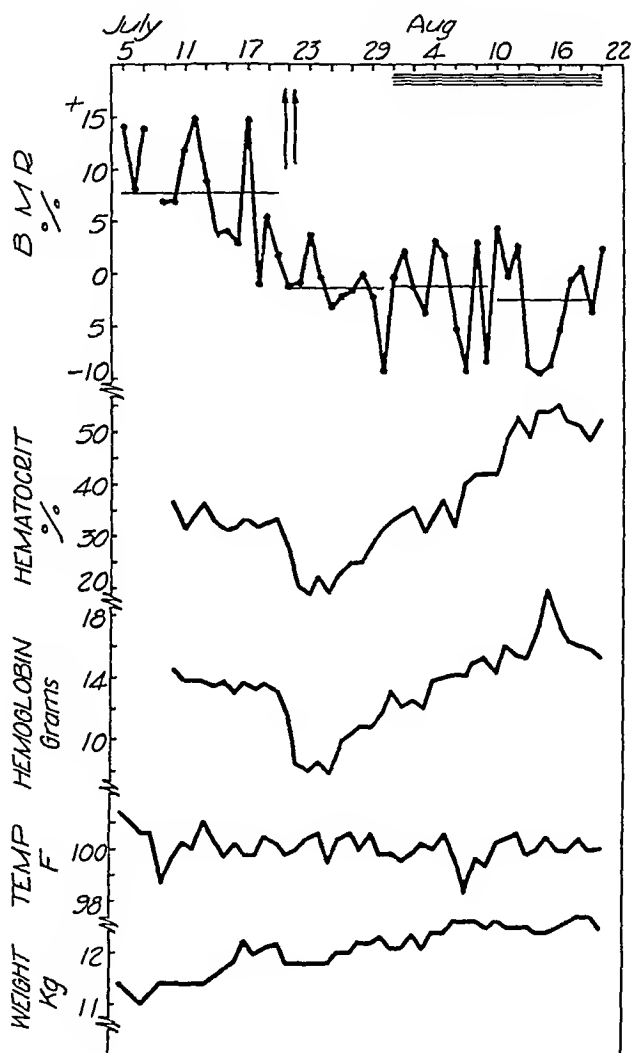


Chart 2 (dog 2) —Two hundred and seventy cubic centimeters of blood was drawn on July 20, and 285 cc on July 21, 1931. Liver extract was given as in the previous instance (dog 1).

mined, but it is assumed for obvious reasons that the animals were storing nitrogen as well as carbon during the period of recovery.

Dog 3 was bled again at a later date, but an acute febrile illness with vomiting, anorexia and loss of weight followed immediately after the bleeding, so that the results of the experiment were completely invalidated.

The literature on the subject under consideration, though not extensive, is in direct contrast to these results. Eberstadt⁷ found that the gaseous metabolism in rabbits with hemorrhagic anemia was increased, and Rolly⁸ reported a similar rise in the oxygen consumption of dogs after bleeding. Logical objections to the work of these investigators

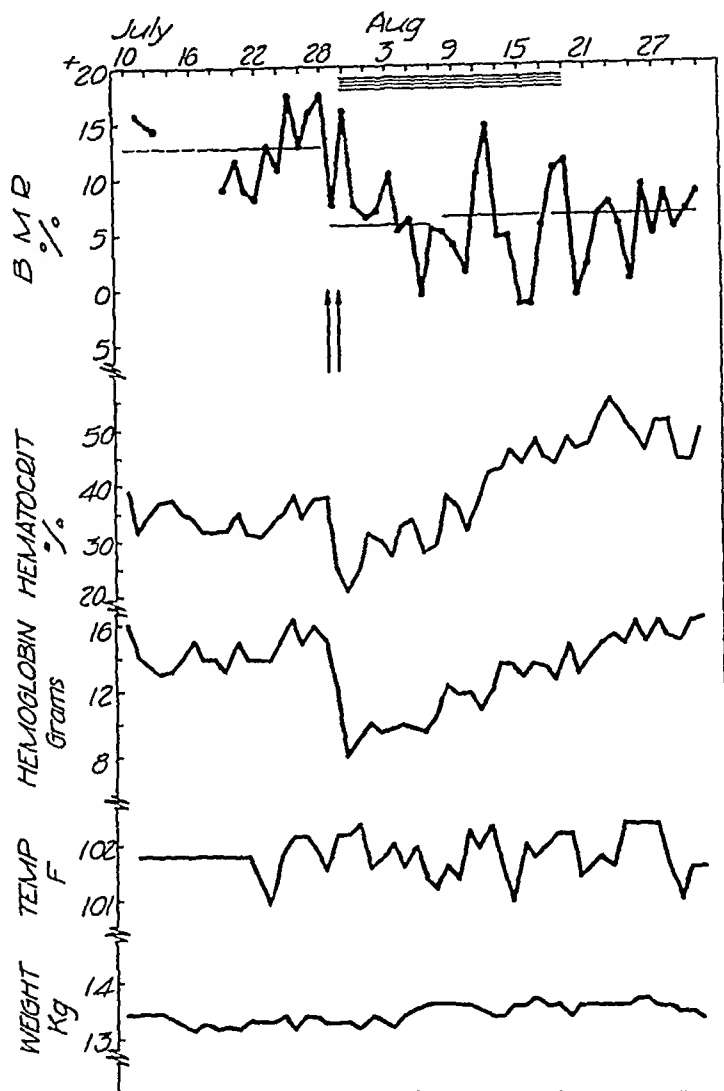


Chart 3 (dog 3)—Three hundred and twenty-five cubic centimeters of blood was drawn on July 28, and 280 cc on July 29, 1931. Liver extract was given for twenty days, starting immediately after bleeding.

can be based on the fact that determinations on controls were few and on the fact that there was no evidence that the animals had been

7 Eberstadt, F. Ueber den Einfluss chronischer experimenteller Anämien auf den respiratorischen Gaswechsel, *Arch f exper Path u Pharmakol* **71** 329, 1913.

8 Rolly, F. Ueber den respiratorischen Gaswechsel bei chronisch anämischen Zuständen, *Deutsches Arch f klin Med* **114** 605, 1914.

trained Hawk and Gies⁹ found a negative nitrogen balance in dogs after severe hemorrhage. However, the blood was let under ether anesthesia, and the arteries were cannulated and tied off after the blood was obtained. The femoral artery or some of its branches were used and were permanently occluded. Some slight increase in the urinary

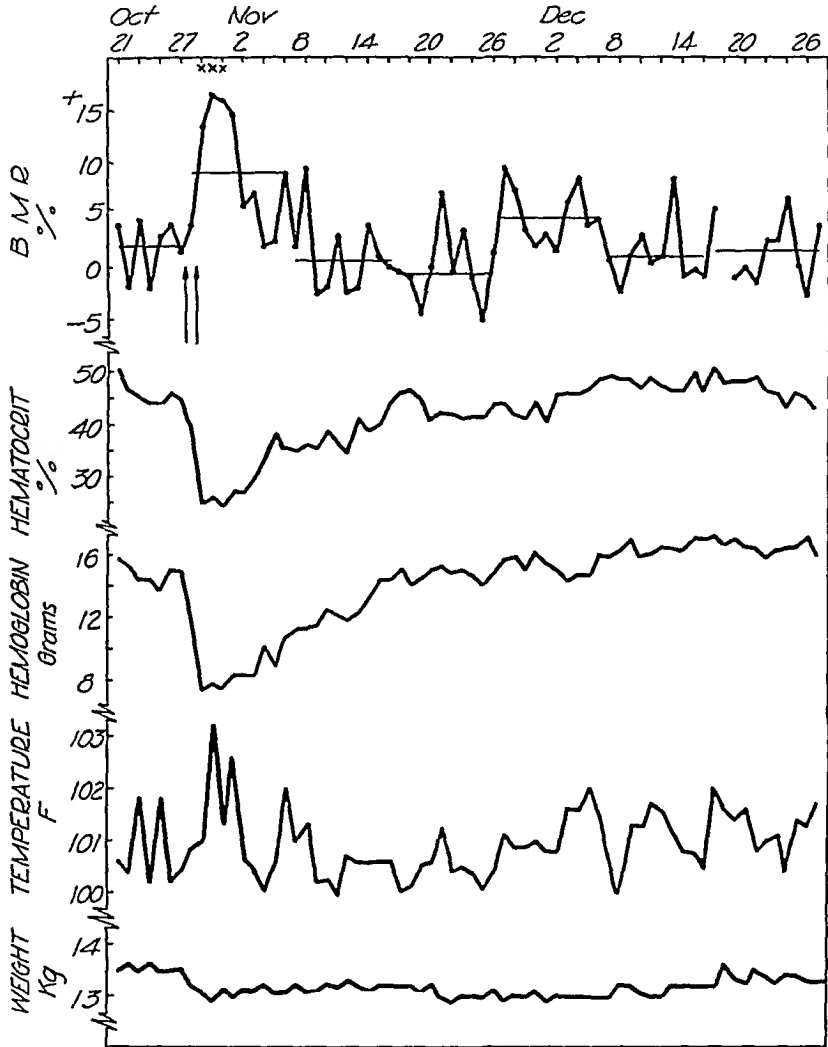


Chart 4 (dog 3) —Three hundred and eighty cubic centimeters of blood was drawn on October 27, and 330 cc on October 28. The dog was acutely ill with fever, vomiting and anorexia for three days after the last bleeding. There was a loss of about 0.5 Kg in weight. This result may be similar to those obtained by Hawk and Gies⁹ in which there was loss of nitrogen following severe or repeated hemorrhages.

nitrogen after bleeding may be due to the "washing out" effect of the large amount of water consumed. The permanent occlusion of such

⁹ Hawk, P. B., and Gies, W. J. The Influence of External Hemorrhage on Chemical Changes in the Organism, with Particular Reference to Protein Catabolism, *Am J Physiol* **11** 171, 1904.

large arteries as the femoral artery might be expected to lead to death of tissue and therefore actual catabolism of protein. Extensive and repeated hemorrhages may influence the dog's general metabolism adversely, while moderate hemorrhages would not. Although the metabolism of all three of the animals remained permanently lower after the bleeding, the following conclusion seems justifiable. During

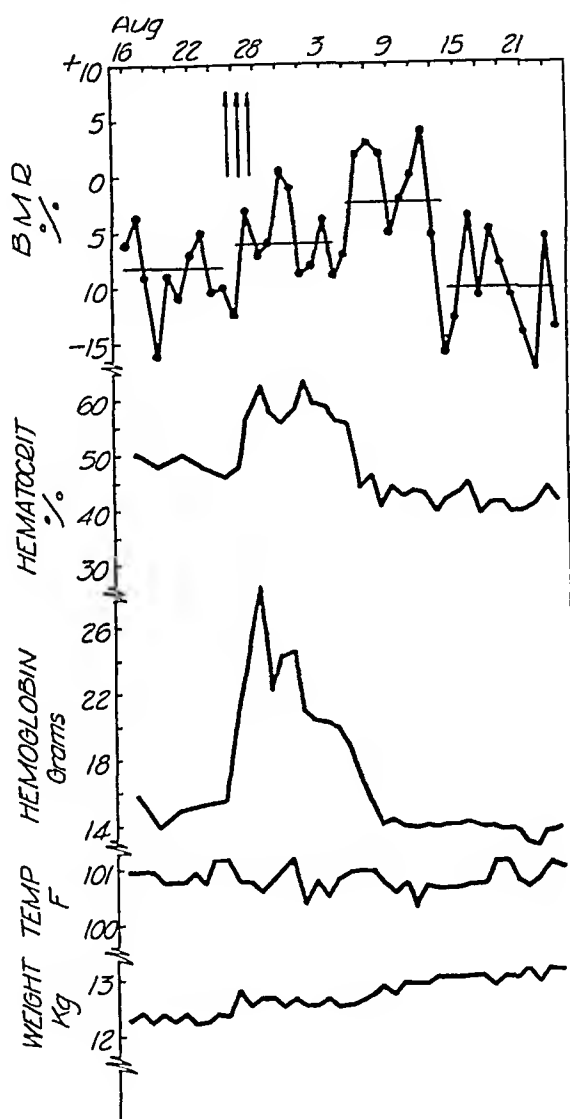


Chart 5 (dog 1)—Blood transfusions were given on August 25, 26 and 27. The amounts were 275, 190 and 155 cc, respectively, and in each instance 50 cc of 25 per cent sodium citrate was used as an anticoagulant.

recovery from acute hemorrhagic anemia of moderate degree in dogs there is a decrease in oxygen consumption which is comparable with that seen in patients with pernicious anemia during the recovery which is induced by liver extract.

Transfusion of Whole Blood—Dogs 1 and 4 were given transfusions of compatible whole blood in quantities equivalent to about

50 cc per kilogram of body weight (charts 5, 6, 7 and 8B) Transfusions were given to dog 1 on three successive days and were begun forty days after the previous experiment with bleeding The weight, blood count and oxygen consumption had reached constant levels before the transfusions were given Dog 4 had not been bled previously, and neither dog had been given a transfusion previously

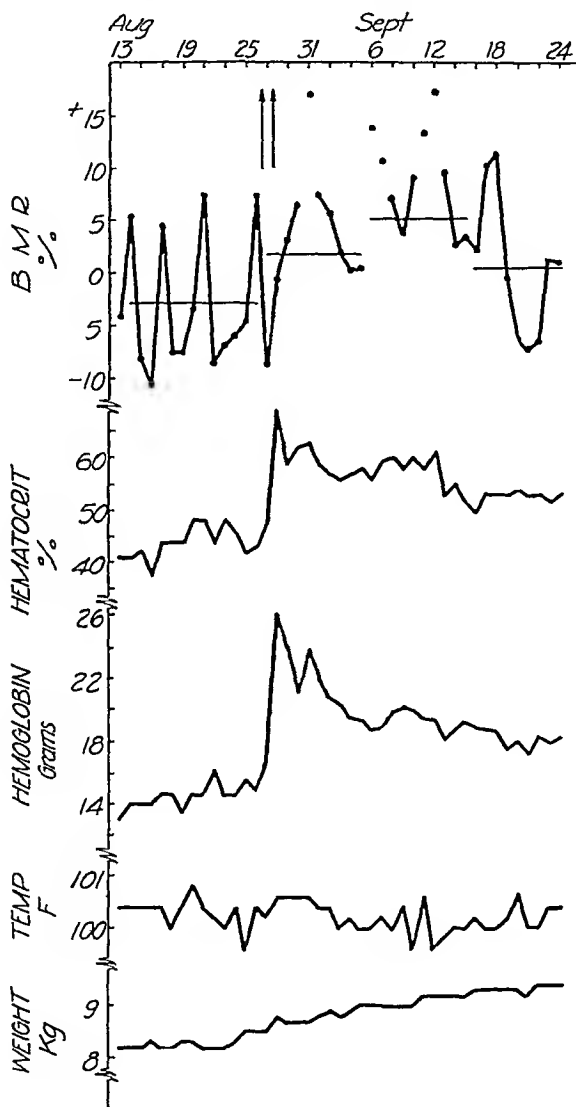


Chart 6 (dog 4) —Transfusions were made on Aug 26 and 27, 1931 The amounts of blood given were 180 and 245 cc Several determinations of basal metabolism were considered to be unsatisfactory because the dog moved These rates are indicated by dots but are not connected by solid lines and were not used in computing averages

The responses in the two dogs were parallel There was an immediate increase in hemoglobin and hematocrit values and in erythrocyte counts The hematocrit values remained fairly constant for ten days in dog 1 and for sixteen days in dog 4 The hemoglobin values seemed

to fall off gradually in both dogs, but the erythrocyte counts paralleled the hematocrit values rather well. Both dogs showed a greater loss of blood during the second period of ten days after transfusion than during the first period of ten days.

The basal metabolic rate increased as the volume of corpuscles decreased. For the first ten days after transfusion the basal metabolic rate was slightly above the control average, 2.3 per cent in dog 1 and

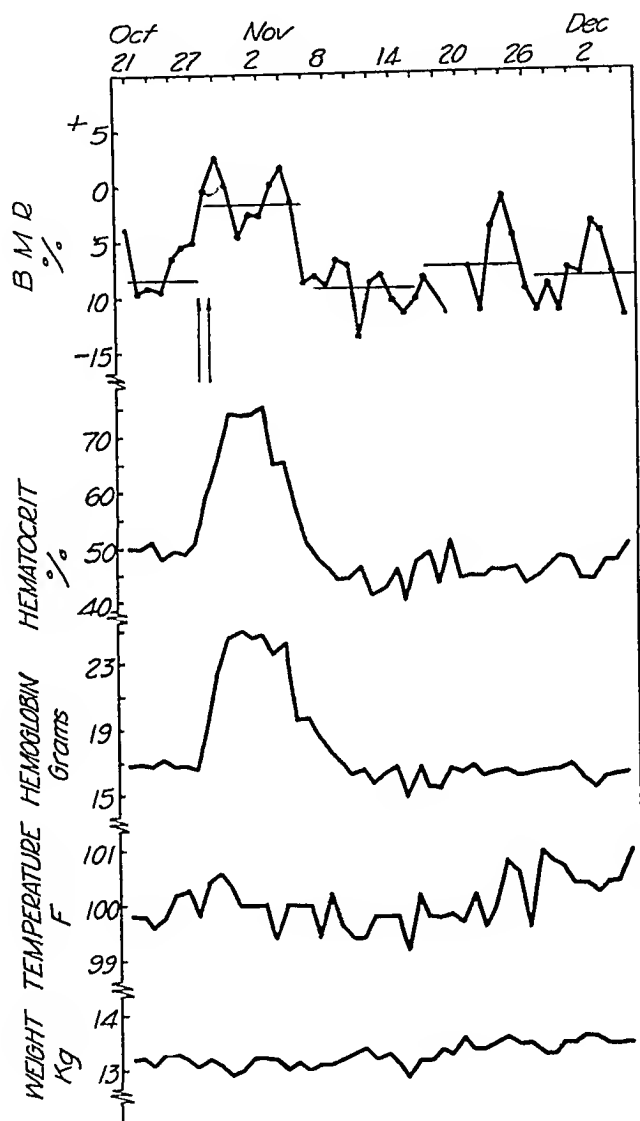


Chart 7 (dog 2)—Two hundred and sixty cubic centimeters of blood was given on October 27 and 330 cc on October 28

4.6 per cent in dog 4. In the second period of ten days the average basal metabolism was 6 per cent above the control in dog 1 and 8 per cent above the control in dog 4. In each dog, the blood count and the oxygen consumption returned approximately to normal during the third period of ten days after transfusion. It is admitted that the differences in basal metabolic rates in these experiments are slight, especially in view of the many variable factors influencing the determination of the

oxygen consumption by the method employed. However, the orderliness and parallelism of the changes in the two animals and especially the correlation between the oxygen consumption and the loss of blood are striking enough to appear significant. Changes in body temperature were slight and bore no apparent relation to the changes in oxygen consumption.

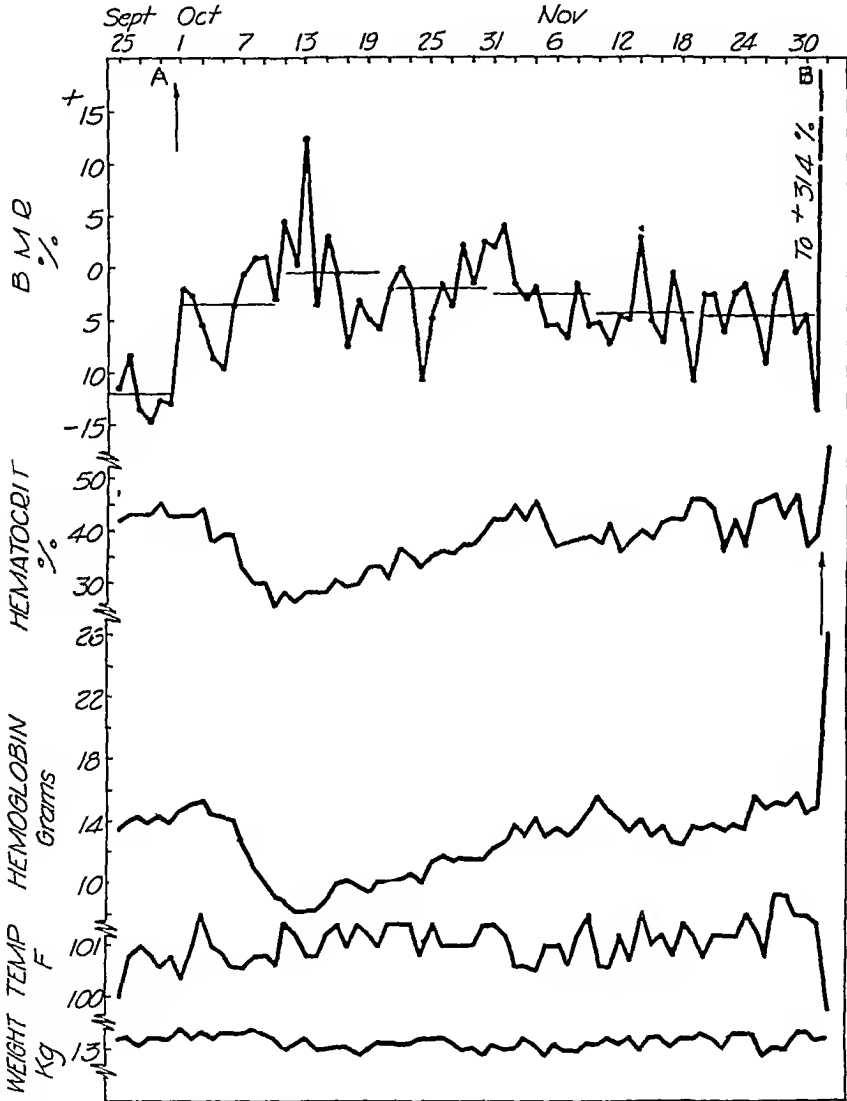


Chart 8 (dog 1) —A, 200 cc of citrated plasma was given intravenously on September 30. B, 375 cc of whole blood was given intravenously on Dec 1, 1931. The dog died on December 2.

A similar experiment was performed in the case of dog 2, but conditions were different in one regard. On Sept 1, 1931, dog 2 received subcutaneous injections of the plasma and hemolyzed corpuscles from 275 cc of compatible blood. On September 30 a further injection of 265 cc of citrated plasma was made intravenously. On October 27 and

28, dog 2 received transfusions totaling 590 cc of whole blood from a different but compatible donor. This transfusion led to the usual immediate increase in the hemoglobin, volume of corpuscles and erythrocyte count, but loss of blood set in on the fifth day instead of after from ten to sixteen days, as had been the case in dogs which had not previously received transfusions. This earlier loss of blood was associated with an earlier increase in the basal metabolic rate. The average basal metabolic rate for the ten days following transfusion was 52 per

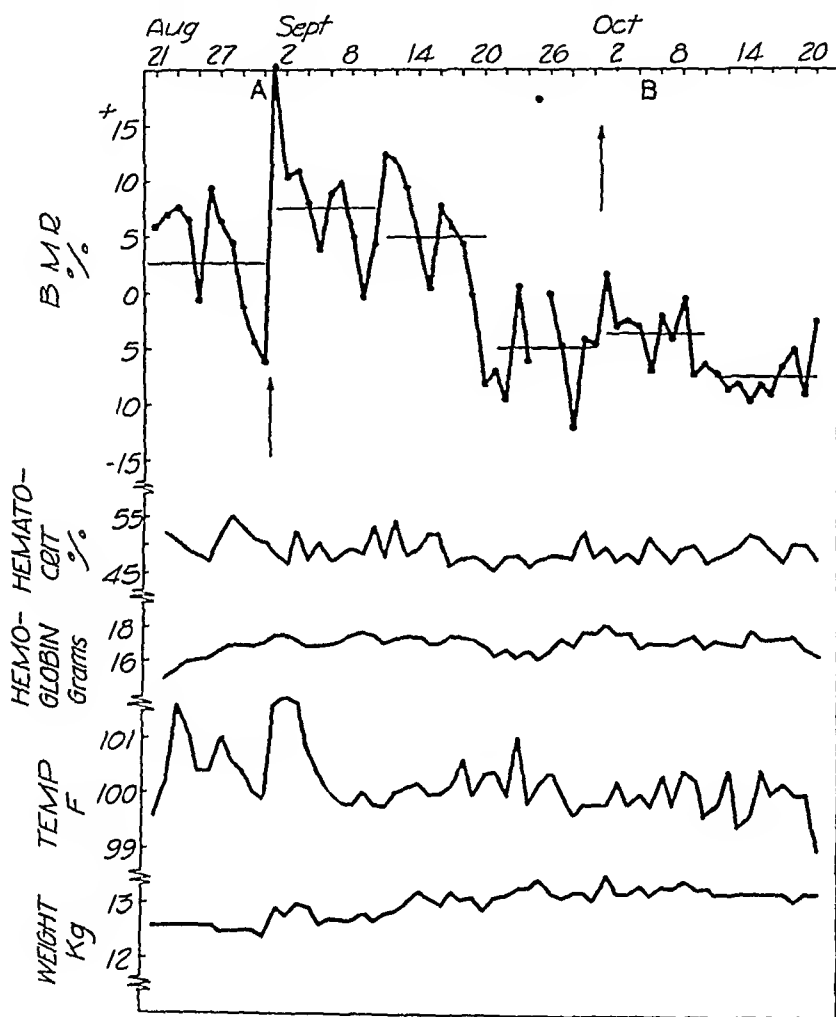


Chart 9 (dog 2) —A, the plasma and hemolyzed corpuscles from 275 cc of blood were injected subcutaneously on September 1. B, 265 cc of citrated plasma was administered intravenously on September 30.

cent above the control average. The average of the results of the determinations made during the second period of ten days showed that the gaseous metabolism was 2.4 per cent below the control average. The data in this experiment lend support to the assumption that there is a causal relationship between the loss of blood and the increase in oxygen consumption.

In an effort to study this process in a more accentuated form, dog 1 was given a transfusion of 375 cc on Dec 1, 1931. Previous trans-

fusions in the case of this dog included intravenous injections of whole blood in amounts of 275, 190 and 155 cc on Aug 25, 26 and 27, 1931, and an injection of 200 cc of citrated plasma on September 30 All of the transfusions were made from the same donor, the blood of which was originally compatible

The basal metabolism, which during the control period had averaged 4.5 per cent below normal, increased to 31.4 per cent above normal on the day after the transfusion With this rise in the gaseous metabo-

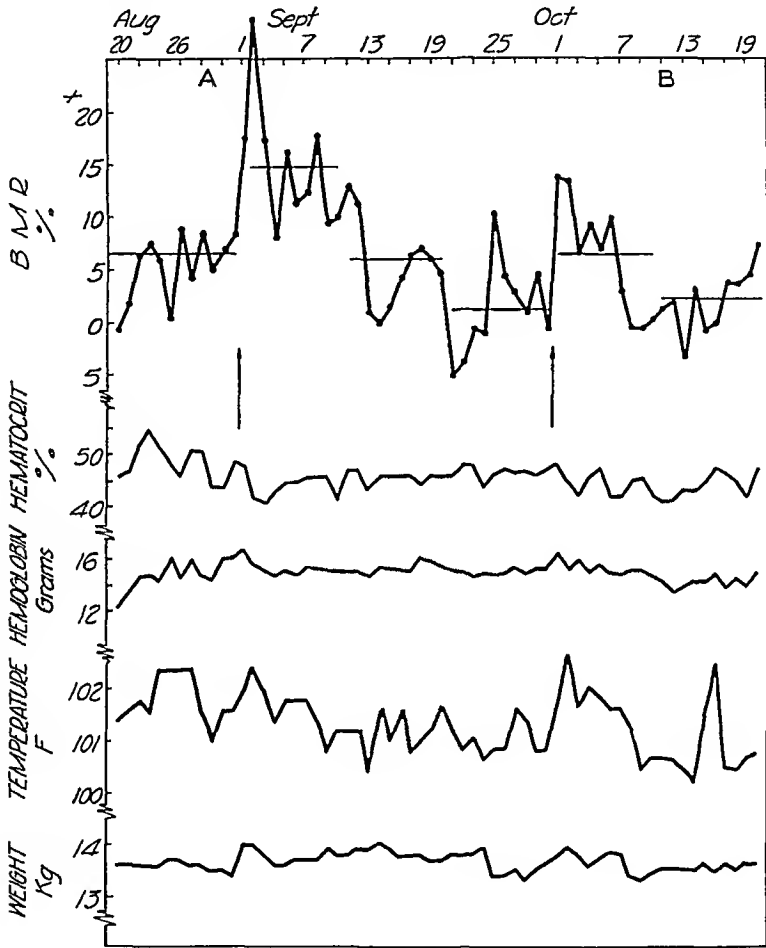


Chart 10 (dog 3) —*A*, the plasma and hemolyzed corpuscles from 325 cc of blood were injected subcutaneously on September 1 *B*, the hemolyzed corpuscles from 320 cc of blood were given subcutaneously on September 20

lism the temperature dropped from 101.5 to 99.8 F Later in the day the dog died Necropsy revealed intense congestion of the spleen, liver and lymph nodes, with dark blood in the gastro-enteric tract and hemorrhages into most of the mucous surfaces Paresis of the caudal half of the body, which appeared soon after the transfusion, was unexplained at necropsy

Hemolyzed Corpuscles and Plasma—In order to speed up the catabolism of the hemoglobin of transfused blood, hemolyzed erythro-

cytes were injected into two dogs (charts 9 *A*, 10 *A* and 11 *A*) The corpuscles were hemolyzed in distilled water, and plasma and hemolyzed corpuscles were injected subcutaneously Dog 2 received 275 cc of whole blood so treated, and dog 3 was given the plasma and hemolyzed corpuscles from 325 cc of blood

There was a prompt outpouring of blood pigments in the urine The urine was black and gave positive qualitative tests for bile pigments and

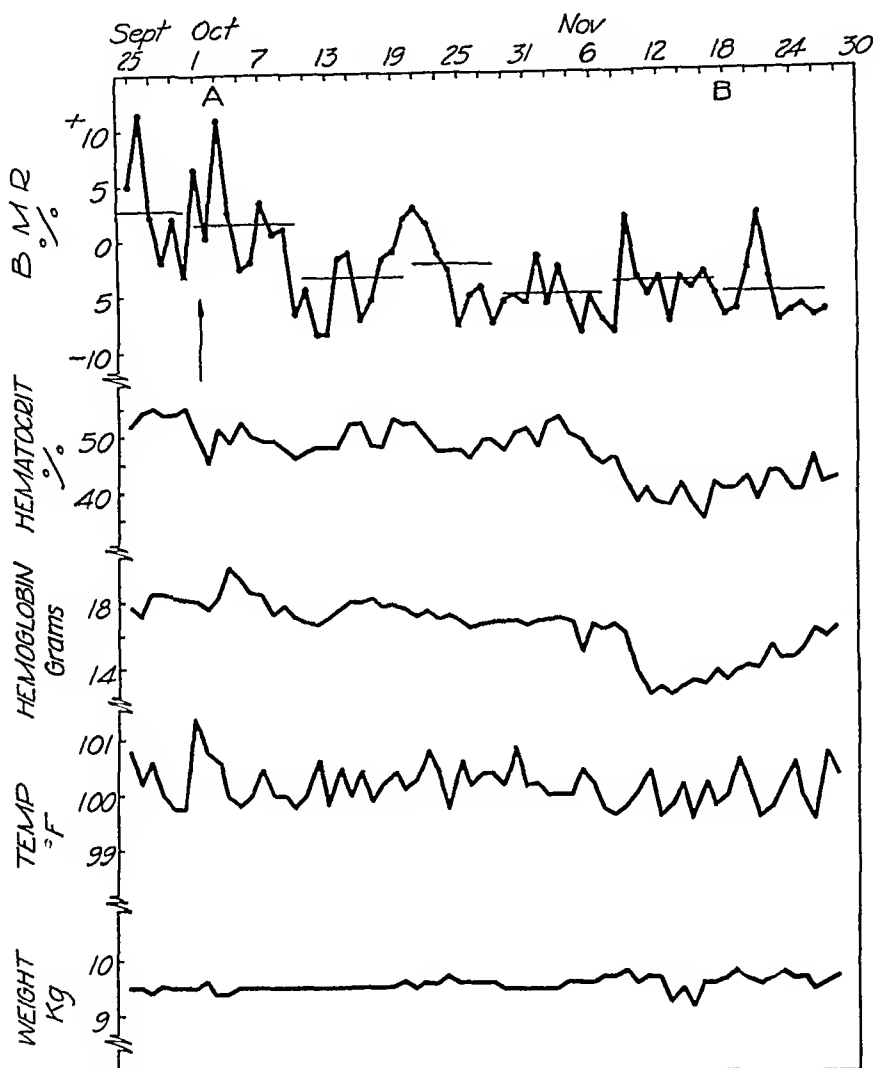


Chart 11 (dog 4) —*A*, the hemolyzed corpuscles from 275 cc of blood were given on September 30 *B*, from October 28 to November 15 almost daily injections of distilled water were made intravenously Thirty cubic centimeters was injected daily for ten days, after which injections of the following amounts were made each day 100, 150, 200, 200, 200, 300, 300, 0 0 and 300 cc Twice the basal metabolic rate was determined at hourly intervals after injections of 300 cc (see text) Hemoglobin appeared in the urine after seven of the injections of distilled water

for hemoglobin There was also rather marked proteinuria There was a slight increase in temperature, but in neither case did the temperature exceed the high point in the control period Following the injec-

tions there was an abrupt rise in the oxygen consumption, which was followed by a gradual fall extending over the succeeding twenty days. The number of erythrocytes and the amount of hemoglobin in the recipient's blood were not affected by this procedure. The urine remained dark for several days.

In these, as in the preceding experiments, the increased oxygen consumption coincided with the period of assumed protein catabolism. Nitrogen balances, however, were not determined.

At a later date dogs 3 and 4 received injections of hemolyzed corpuscles without plasma (charts 10 *B* and 11 *A*). The amounts were smaller, hemoglobin from 180 cc of blood injected into dog 3 and from 275 cc of blood injected into dog 4. The results were similar to those in the preceding experiments except that the increase in oxygen consumption was less marked in spite of the fact that the increase in temperature was greater.

An attempt was made to study the effects of *in vivo* hemolysis by distilled water in dog 4 (chart 11 *B*). Distilled water was injected intravenously in amounts varying from 30 to 300 cc. Hemoglobin appeared in the urine on seven occasions, and there was a loss of about 5 Gm of hemoglobin per hundred cubic centimeters of blood during a period of nine days. However, the oxygen consumption as determined twenty-two hours after the injections remained normal. On two days determinations made at hourly intervals after the injections showed maximum increases of 14 and 69 per cent. On the second day the increase lasted at least ten hours, but there were a chill and an elevated temperature which invalidated the result. On the first day, which presents no doubt the more accurate picture of the changes, the control basal metabolic rate was 3.5 per cent below normal. After the rapid injection of 300 cc of warm distilled water the rates at hourly intervals were as follows: plus 10.4, plus 9.4, plus 8.7, plus 8.9, plus 2.3 and plus 6.4 per cent. Here, as in the preceding experiments, hemoglobinuria was accompanied by proteinuria. It is recognized, of course, that the nitrogen appearing in the urine as protein or amino-acids must be deducted from the total nitrogen in order to estimate catabolized protein nitrogen.

Plasma Administered Intravenously.—Citrate plasma was injected intravenously in dogs 1 and 2 (charts 8 *A* and 9 *B*). The results were in part unexpected. Dog 2 received 265 cc of citrated plasma on Sept. 30, 1931. On the day following the injection, the oxygen consumption was about 6 per cent greater than on the day preceding the transfusion, while the average for the ten days following transfusion was about 1 per cent higher than the control average. The hemoglobin, hematocrit value and erythrocyte count were unaffected by this pro-

cedure The dog had had only one previous injection of plasma and hemolyzed corpuscles from the same donor

The case of dog 1 was different (chart 8 A) Intravenous injection of 200 cc of citrated plasma was made as in dog 2 The basal metabolic rate, which was 13 per cent below normal on the day before the injection, was only 2 per cent below normal on the following day The average oxygen consumption for the first ten days after the injection of plasma was 85 per cent above the control level, while the average for the second period of ten days was 115 per cent above the control level This increase in oxygen consumption was associated with a loss of hemoglobin from about 15 to about 8 Gm per hundred cubic centimeters of blood and a corresponding decrease in hematocrit value and erythrocyte count Unfortunately, estimations of the urobilin and urobilinogen content of the stools and urine and nitrogen balances were not made, so that it is not possible to attribute the loss of blood definitely to hemolysis Recovery of the blood elements was complete, however, a circumstance which makes it unlikely that the loss of blood was due to aplasia of the bone marrow

In these experiments it appears that destruction of blood was produced in one animal and not in the other It further appears that a rather nicely controlled experiment showing the effect of the destruction of blood on the total oxygen consumption has been unwittingly accomplished The results are in complete accord with the general thesis, i e, that the oxygen consumption is increased by increased endogenous protein catabolism

Diabetes Caused by the Administration of Phlorhizin—Phlorhizin diabetes seemed to present the most ideal situation for putting the previously suggested general thesis to a crucial test (charts 12, 13 and 14) In the phlorhizinized animal endogenous protein catabolism proceeds at a greater rate than in any other nonfatal condition that I know As the effects of phlorhizin disappear, the animal is left in good health, except that his protein is much depleted Such a condition should therefore be ideal for the study of the effects of endogenous protein catabolism as well as of the effects of marked retention of nitrogen in the laboratory animals It was demonstrated by Rubner¹⁰ that the specific dynamic effect of catabolized protein of endogenous origin could account for the marked increase in oxygen consumed by the fasting phlorhizinized dog From such calculations Lusk concluded that protein of endogenous origin exerts the same specific dynamic effect as a similar amount of exogenous protein To my knowledge, no one has previously studied the oxygen consumption of animals during the period of nitrogen storage in the recovery from diabetes due to the administration of phlorhizin

¹⁰ Rubner, M Die Gesetze des Energie verbruchs bei der Ernahrung, Leipzig, Franz Deuticke, 1902, p 370, quoted by Lusk,⁶ p 282

Dog 2 was given the regular diet up to and including Dec 15, 1931. After the determination of the basal metabolism on December 16, 1 Gm of phlorhizin was injected subcutaneously. No more food was given for eight days, during which there was evidence of marked endogenous protein catabolism. The D N ratio reached only 1.93, so that the animal was not completely phlorhizinized. On December 24, food, consisting of 225 Gm of bread, 250 cc of milk and 20 Gm of bone meal or 4.6 Gm of nitrogen, was allowed. The oxygen con-

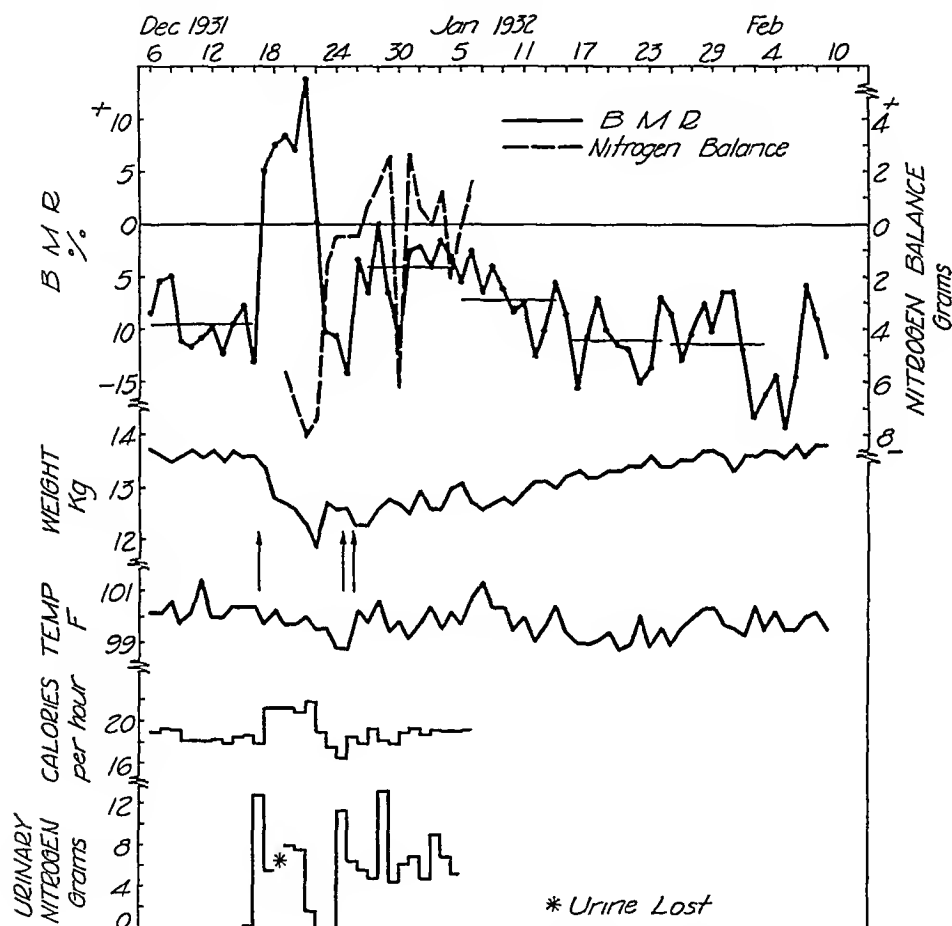


Chart 12 (dog 2) —The first arrow (from left to right) indicates the beginning of the fast and the administration of 1 Gm of phlorhizin subcutaneously on December 16. The second arrow indicates when food was first given, on December 24, 225 Gm of bread, 250 cc of milk and about 20 Gm of bone meal. The third arrow indicates the return to the normal diet. The nitrogen balance is not accurate, since fecal nitrogen and the nitrogen lost in hair were not determined. The irregularity in the output of urinary nitrogen was caused by the fact that the dog had been conditioned not to urinate in a cage.

sumption, which had been falling to about parallel with the fall in nitrogen catabolism, continued to fall with the ingestion of the aforementioned amount of protein. From December 25 to the end of the experiment the animal was given its regular diet of 150 Gm of chopped

raw beef lung, 225 Gm of bread, 250 cc of milk and 20 Gm of bone meal, a total of 68 Gm of nitrogen daily After the return to a normal diet there was an immediate increase in the amount of urinary nitrogen with a similar increase in gaseous metabolism (chart 12) Nitrogen retention was not constant or marked It seemed evident that the animal was continuing to break down protein instead of storing it This

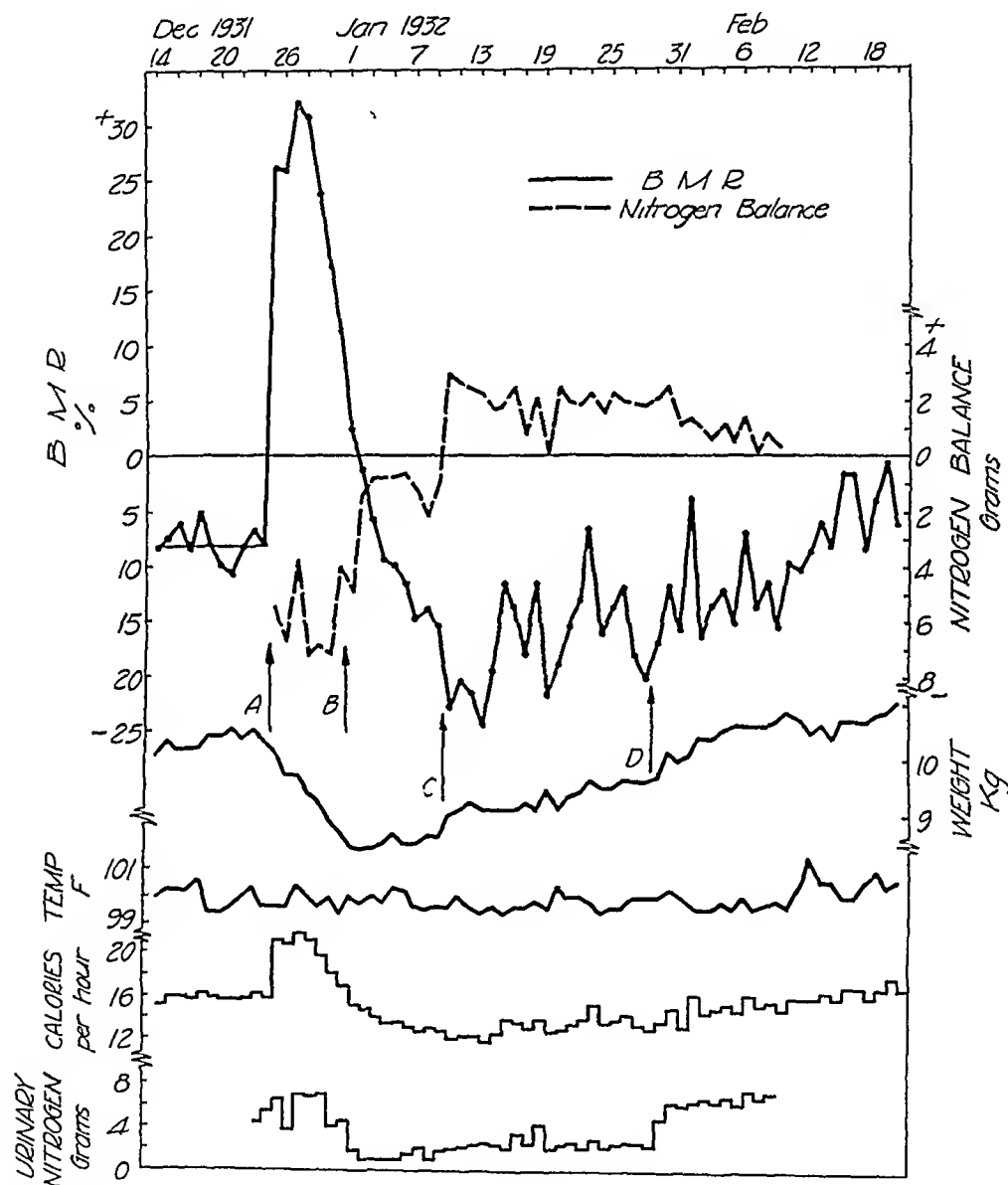


Chart 13 (dog 4)—Arrows indicate the following A, subcutaneous injection of 1 Gm of phlorhizin and the beginning of the fast, B, from 50 to 200 Gm of sugar daily (total 1,050 Gm), C, 200 Gm of bread, 20 cc of milk and about 20 Gm of bone meal daily, D, 200 Gm of meat was added to the diet Again the nitrogen balance did not include nitrogen lost in the feces or hair

may have been due to the fact that the stores of glycogen were empty when realimentation with a mixed diet occurred An attempt was made to control this factor in the succeeding experiments

In the case of dog 4 (chart 13) the procedure was the same, except that on the seventh day after phlorhizin was administered, 50 Gm of dextrose was given by mouth. On the six succeeding days the animal received 100 Gm of dextrose daily and then 200 Gm daily for two days. During this time the gaseous metabolism and the urinary nitrogen continued to decrease. The average basal metabolic rate during the

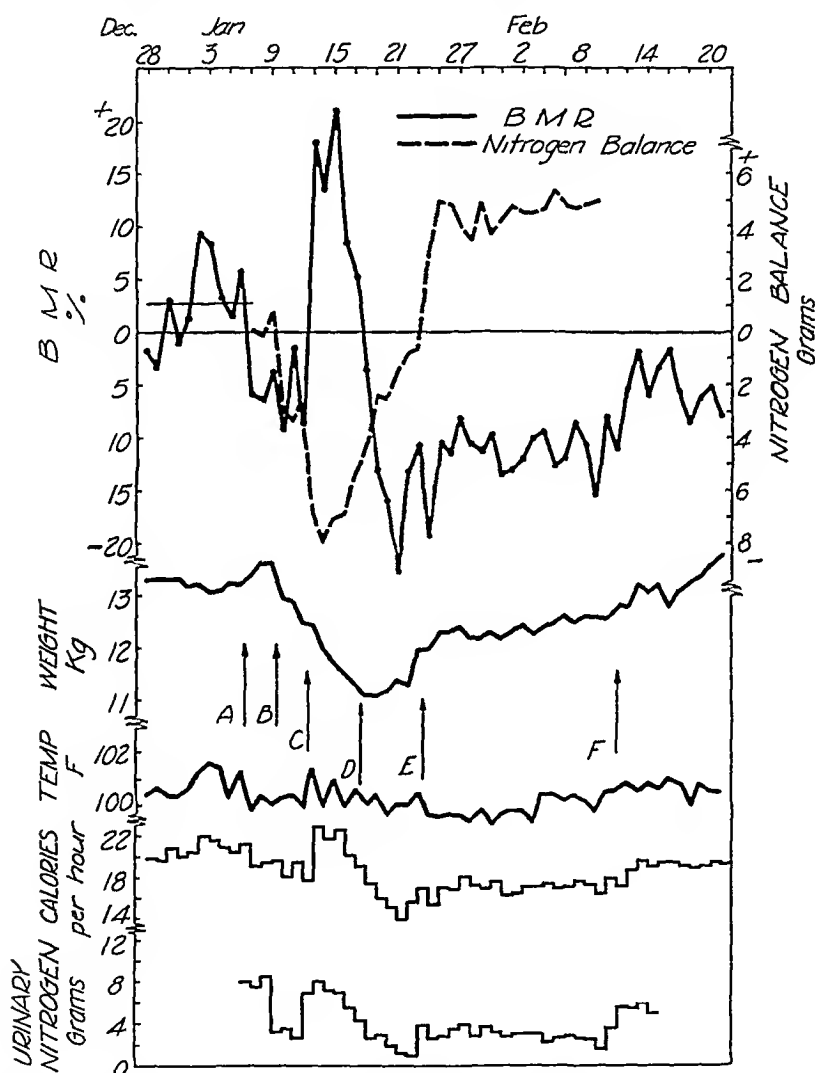


Chart 14 (dog 3) —The arrows indicate the following A, the dog was moved from regular animal quarters to the cage in the metabolism room, B, the fast was begun, C, 1 Gm of phlorhizin was given, D, from 100 to 300 Gm of sugar (total, 2,000 Gm) was given, E, 300 Gm of bread, 350 cc of milk and 20 Gm of bone meal were given daily, F, 200 Gm of meat was added

control period was 8.1 per cent below normal. During the period of increased protein catabolism after phlorhizin the metabolic rate reached 32.1 per cent above normal, but the oxygen consumption fell to 15.5 per cent below normal, as endogenous protein was spared by the feeding of sugar. On December 9 the diet was changed to 200 Gm of bread,

250 cc of milk and 20 Gm of bone meal or 4.56 Gm of nitrogen a day. This diet was attended by marked and consistent nitrogen retention and a further fall in the oxygen consumption to 24.4 per cent below normal. This second fall in gaseous metabolism which occurred when the animal was receiving a diet low in proteins is not understood, since the actual amount of nitrogen in the urine was greater than it had been on the preceding days when only carbohydrate was contained in the diet. Special attention is directed to the fact that in this animal the basal metabolic rate fell from plus 32.1 to minus 24.4 per cent, a total excursion of 56.5 per cent, without change in temperature. The decrease from plus 32.1 to minus 15.5 per cent appeared to be caused entirely by a drop in the catabolism of endogenous protein.

In dog 3 the procedure and results were almost exact duplicates of those in dog 4 (chart 14).

The following explanation is offered for the results in all of the experiments described.

Endogenous protein, when catabolized, exerts the same specific dynamic effect as would a similar amount of ingested protein. The difference is that the effect of exogenous protein can be avoided to a great extent by making determinations of the basal metabolic rate only in the postabsorptive period. Endogenous protein catabolism, on the other hand, is a continuous process, and some of the amino-acids so derived exert their effect throughout the day.

The explanation for the lowered gaseous metabolism during the storage of nitrogen is not quite so clear but no doubt depends in part at least on the fact that stored amino-acids exert no specific dynamic effect. From numerous data it seems probable, though not proved, that the lowered oxygen consumption during the storage of nitrogen is due not so much to the storage of nitrogen per se as to a lowered total endogenous catabolism of protein during the postabsorptive period when storage is in progress.

Numerous data in the literature support this thesis directly or indirectly. Only a few will be mentioned. Rubner¹¹ and Hoobler¹² independently showed that stored protein does not exert a specific dynamic effect. Lee and Gagnon¹³ showed that rats growing rapidly under the influence of the growth-promoting hormone from the anterior pituitary lobe have a lowered basal metabolism as referred to weight or surface area. The realimentation following a fast is not attended

¹¹ Rubner,¹⁰ p. 246, quoted by Lusk,⁶ p. 297.

¹² Hoobler, B. R. The Protein Need of Infants, *Am J Dis Child* **10** 153 (Sept.) 1915.

¹³ Lee, M. O., and Gagnon, J. Effect of Growth Promoting Extracts of the Anterior Pituitary on Basal Gaseous Metabolism in Rats, *Proc Soc Exper Biol & Med* **28** 16, 1930.

by an immediate return of the oxygen consumption to the prefasting level (Kleitman¹⁴ and Anderson and Lusk¹⁵)

Evidence that increased protein catabolism is associated with an augmented gaseous metabolism is also to be found in the literature Du Bois¹⁶ and his co-workers demonstrated that the increased oxygen consumption in febrile diseases was more or less proportional to the degree of endogenous protein catabolism which was present For example, for a given elevation in temperature typhoid fever usually presented a greater protein catabolism and a greater oxygen consumption than did pulmonary tuberculosis Similarly, increases in endogenous protein catabolism¹⁷ and in oxygen consumption occur coincidentally in the first few days of a fast and possibly during the premortem rise in nitrogen excretion Wilder, Boothby and Beeler¹⁸ demonstrated a definite relationship in diabetes between the amount of protein in the diet and the basal metabolism Heinbecker¹⁹ found that the gaseous metabolism of Eskimos was considerably higher than that of people living in the temperate zone At the Russel Sage Institute²⁰ two Arctic explorers were kept on a diet of meat for a year After six weeks the basal metabolism had increased slightly, but at the end of a year it was back to the level which had been observed for a mixed diet There was a suggestion that the specific dynamic action of protein increased after long periods on diets of meat In most instances the diets were much higher in fat than in protein There is a possibility, of course, that the presence of acetone influenced the results obtained by the investigators, who studied subjects receiving diets high in fat and relatively high in protein but without carbohydrate

SUMMARY

1 In pernicious anemia the basal metabolic rate decreases during periods of rapid regeneration of blood

2 In leukemia the total oxygen consumption is increased during the increased catabolism of endogenous protein induced by irradiation

14 Kleitman, N Basal Metabolism in Prolonged Fasting in Man, *Am J Physiol* **77** 233, 1926

15 Anderson, R J, and Lusk, G Animal Calorimetry The Interrelation Between Diet and Body Condition and the Energy Production During Mechanical Work, *J Biol Chem* **32** 421, 1917

16 Du Bois, E F The Basal Metabolism in Fever, *J A M A* **77** 352 (July) 1921

17 Lusk,⁶ p 78

18 Wilder, R M, Boothby, W M, and Beeler, C Studies of the Metabolism of Diabetes, *J Biol Chem* **51** 311, 1922

19 Heinbecker, P Studies on the Metabolism of Eskimos, *J Biol Chem* **80** 461, 1928

20 McClellan, W S, Spencer, H J, and Falk, E A Clinical Calorimetry XLVII Prolonged Meat Diets with a Study of the Respiratory Metabolism, *J Biol Chem* **93** 419, 1931

3 The destruction of erythrocytes by phenylhydrazine in polycythemia vera is attended by an increase in gaseous metabolism

4 In dogs the oxygen consumption is decreased during recovery from moderately severe acute hemorrhagic anemia

5 Compatible blood transfused into dogs is lost from the peripheral circulation at varying rates. The rapidity of loss of blood seems to be increased in successive transfusions. The basal metabolic rate of the dog is increased during the period of loss of blood

6 The pigment from hemolyzed blood is rapidly excreted by dogs, and again the catabolic process is attended by an increase in gaseous metabolism. The increased metabolism occurs whether the blood is hemolyzed *in vivo* or is obtained from another animal

7 The injection of citrated plasma into dogs is sometimes attended by a delayed loss of blood in the recipient, and this loss of blood appears to cause an increase in gaseous metabolism

8 Phlorhizin diabetes in the dog is associated with a great increase in endogenous protein catabolism which is followed under certain conditions by marked storage of nitrogen. The oxygen consumption in the phlorhizinized animal parallels the endogenous protein catabolism

HEPATIC FUNCTION

I NONCALCULOUS AND CALCULOUS CHOLECYSTITIS

A CANTAROW, MD

PHILADELPHIA

Increasing recognition of the valuable information which may be derived from studies of hepatic function has resulted in the accumulation of a large quantity of data in this connection in recent years. In my experience, however, too little emphasis has been placed on such studies in the field in which they are of greatest value, namely, in the pre-operative study of patients with disease of the gallbladder and bile ducts. This point was stressed in a previous report¹ of a study of 234 patients with calculous and noncalculous cholecystitis, 70 of whom presented hyperbilirubinemia or bromsulphalein retention or both. The present report is a continuation of that study, with a more detailed presentation of the findings in a much larger series of patients.

During the years from 1931 to 1933, various studies of hepatic function were performed in 512 cases of cholecystitis and cholelithiasis, 49 of these were acute noncalculous cholecystitis, 288, chronic noncalculous cholecystitis, and 138, calculous cholecystitis, and in 37 cases, stones were present in the common bile duct. Of the several observations that were made, only the following are included: (1) qualitative van den Bergh reaction, (2) serum bilirubin concentration (quantitative van den Bergh method), (3) bromsulphalein retention (dosage of 2 mg per kilogram expressed as thirty minute retention), (4) plasma cholesterol concentration (method of Myers and Wardell) and (5) urinary urobilinogen (method of Wallace and Diamond). In my experience, the normal range of values by the methods employed are as follows: bromsulphalein retention, 0 per cent, plasma cholesterol, from 140 to 200 mg per hundred cubic centimeters, urobilinogen in urinary dilution to 1:20, serum bilirubin concentration, from 0.1 to 1 mg per hundred cubic centimeters of serum or plasma. I think that the normal serum bilirubin values usually quoted in the literature are far too low. The most frequent source of error lies in the fact that unless the test is carefully performed according to the procedure suggested by Thannhauser and Andersen, varying quantities of bilirubin are adsorbed by the protein precipitate and are consequently eliminated from the calculation. In a large series of determinations on normal persons I obtained the following results: from 0.1 to 0.5 mg in about

From the Laboratory of Biochemistry, Jefferson Hospital

1 Cantarow, A. The van den Bergh Reaction and the Bromsulphalein Test in the Estimation of Hepatic Functional Impairment, *Am J M Sc* **184** 228, 1932

60 per cent, from 0.51 to 0.8 mg in about 35 per cent and from 0.81 to 1 mg in about 5 per cent. Another point in this connection deserves special emphasis. Hunter² and later Rabinowitch³ called attention to an error in the original calculation of the van den Bergh unit. Rabinowitch stated that

The color of the original artificial standard which was meant to match that produced by 1 unit of bilirubin corresponded to that obtained with a mixture of 10 cc of alcohol, 25 cc of diazo reagent and 0.05 mg of bilirubin. Since 12.5 cc of solution contained 0.05 mg of bilirubin, the true unit corresponds to a 1:250,000 and not to a 1:200,000 dilution of bilirubin. Expressed more exactly, the true unit corresponds to 0.4 and not 0.5 mg of bilirubin per 100 cc of blood.

TABLE 1—*Acute Cholecystitis*

Case	Date	Direct Van den Bergh	Serum Bilirubin*	Brom sulphalein Retention†	Plasma Cholesterol*	Urobilinogen in the Urine
1	4/ 7/32	0	1.6	0	162	1.10
	4/11/32	+	6.0	90		0
	Operation 4/14/32	0	1.12	0	146	1.30
2		+	1.5	0		1.10
3		+	9.1	80	122	1.60
4		+	1.3	60	104	
5		0	0.9	5	150	
6		+	2.05	100	126	0
7	12/ 1/32	+	2.0	50	125	1.40
	12/ 7/32	0	0.2	0		
8		0	0.65	5		
9	4/ 4/33	0	0.8	25	256	
	4/ 9/33	0	0.4			
10		0	1.94	0		
11	4/18/33	+	4.25	50	274	1.30
	4/25/33	+	6.0	90		
	5/ 2/33	+	2.5	5		
	5/19/33	0	0.6	0		
12	11/ 8/33	0	0.96	20		
	11/14/33	0	0.52	0		1.20
13		0	0.16	15	150	1.10
Cases			Serum Bilirubin*	Bromsulphalein Retention†	Plasma Cholesterol*	Urobilinogen in the Urine
36			0.12-0.88	0	124-196	0.1-2.0

* Expressed in milligrams per hundred cubic centimeters

† Expressed as percentage

This obvious error has apparently been overlooked by the great majority of workers in this field.

EXPERIMENTAL RESULTS

Acute Cholecystitis—In the group of 49 cases of acute cholecystitis, essentially normal findings were obtained by all methods in 36 instances, with the exception of slightly subnormal cholesterol values (from 124 to 132 mg) in 4 cases. Disturbance of hepatic function was suggested by one or more of the methods employed in 13 cases in this group (26.5

² Hunter, G. The Determination of Bilirubin by Diazo Reagents, *Brit J Exper Path* **11** 407, 1930.

³ Rabinowitch, I. M. The Renal Threshold of Bilirubin, *J Biol Chem* **97** 163, 1932.

per cent) The detailed findings are presented in table 1 Hyperbilirubinemia (from 1.3 to 6 mg) was present at some time in 8 cases, bromsulphalein retention in 11, hypercholesteremia in 2, hypocholesteremia in 4 and urobilinuria in 4 The occurrence of hyperbilirubinemia without retention of dye was noted in 3 cases, and retention of dye without hyperbilirubinemia in 5 cases

TABLE 2—*Chronic Cholecystitis Cases with Retention of Bromsulphalein Without Hyperbilirubinemia*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Brom sulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1		0	0.9	10		1.20
2		0	0.83	80	186	1.40
3		0	0.37	10	117	
4		0	0.5	10		
5		0	0.69	60	121	1.50
6		0	0.72	5		
7		0	0.4	5		
8		0	0.98	10	185	1.20
9		0	0.74	5		
10		0	0.37	5		1.10
11	1/20/33	0	0.8	100		
	1/22/33	0	0.4	5		
12		0	0.8	10	228	
13		0	0.8	5		
14		0	0.82	20		
15		0	0.65	5	124	
16	1/24/33	0	0.4	10		
	1/30/33	0	0.25	0		
17		0	0.8	5	123	
18		0	0.6	10	146	
19		0	0.9	10	192	
20		0	0.4	10		
21		0	0.9	5		
22	3/ 7/33	0	0.6	5	224	
	4/19/33	+	1.5	5		
	5/ 3/33	+	7.5	100	198	
	5/ 9/33	+	2.7	5		
23		0	0.7	5	148	
24		0	0.3	5	135	
25		0	0.7	5		
26		0	0.8	25	148	0
27		0	0.5	20	186	1.20
28		0	0.51	10		
29		0	0.64	25	73	1.60
30		0	0.24	10	148	1.20
31		0	0.69	10	192	
32		0	0.81	20	136	1.40

Chronic Noncalculous Cholecystitis—Essentially normal findings were obtained in 212 of 288 patients with chronic noncalculous cholecystitis (table 5) Evidence suggestive of hepatic functional impairment was noted in 76 cases in this group (26.3 per cent) Retention of bromsulphalein (from 5 to 100 per cent) without hyperbilirubinemia was present at some time in 32 cases (table 2), hyperbilirubinemia (from 1.1 to 3 mg) and retention of dye (from 5 to 100 per cent) in 29, and hyperbilirubinemia (from 1.08 to 1.5 mg) without retention of dye, in 15 cases Hypercholesteremia (from 224 to 279 mg) was noted in 4, hypocholesteremia (from 73 to 136 mg), in 15, and urobilinuria (from 1.30 to 1.200), in 16 cases

TABLE 3—*Chronic Cholecystitis Cases with Retention of Bromsulphalein and Hyperbilirubinemia*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Brom sulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1		0	1.1	10		
2	8/31/32	+	2.2	45	136	1.80
	9/ 5/32	0	0.63	5		
3		0	1.16	10	164	1.10
4		0	1.12	15	144	
5		0	1.45	5		
6	5/22/32	+	3.0	25	184	1.200
	6/ 8/32	0	0.81	10		1.100
7		0	1.3	30		
8		0	1.2	10	126	1.20
9	1/ 4/33	+	1.8	40		1.100
	1/10/33	0	0.3	5		
10		0	1.1	5	174	0
11		0	1.57	5		1.30
12		0	1.1	5		1.10
13		+	1.6	30		
14		+	2.5	20		1.20
15		0	1.1	5	163	
16		0	1.1	100		
17		+	1.7	50		
18		+	1.2	20	128	1.40
19		+	2.0	10		
20		0	1.3	10	147	1.75
21		+	1.8	20		1.40
22		0	1.4	10	154	
23		0	1.2	10		1.40
24		+	2.1	10		
25		0	1.6	20	141	1.60
26		+	1.9	10	168	
27		+	2.4	30		
28		+	2.3	40	106	1.80
29		0	1.3	10		1.20

TABLE 4—*Chronic Cholecystitis Cases with Hyperbilirubinemia without Retention of Bromsulphalein*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Brom sulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1		0	1.08	0	161	1.10
2		0	1.43	0		
3		0	1.2	0	95	1.20
4		0	1.2	0	272	1.20
5		0	1.5	0		
6		0	1.2	0		
7		+	1.2	0	197	
8		0	1.1	0	279	
9	5/13/33	0	1.2	0		
	5/19/33	0	0.5	10		
10		0	1.2	0		
11		0	1.12	0	104	1.40
12		0	1.3	0		
13		0	1.1	0	174	1.20
14		0	1.46	0	189	
15		0	1.28	0	162	1.10

TABLE 5—*Chronic Cholecystitis Cases with Essentially Normal Findings*

Cases	Serum Bilirubin	Bromsulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
212	0.24-0.91	0	134-200	0-1.40

TABLE 6—*Calculous Cholecystitis*

Case	Date	Direct Van den Bergh	Serum Bilirubin	Brom sulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1	1/ 5/32	+	4 0	20	194	1 20
	1/ 9/32	+	2 0	0		
2		+	2 2	35	121	
3	1/23/32	+	1 2	90		
	1/23/32	+	4 04	100	106	1 100
	3/ 9/32	0	0 6	0		
4	1/29/32	0	1 32	0	93	1 30
	2/ 4/32	0	1 08	0		
5		+	3 2	100		1 50
6	2/ 3/32	+	2 68	55	119	
	2/10/32	0	0 52	0		
7	2/23/32	+	1 28	15	93	1 20
	2/23/32	0	0 75	0	102	
	3/ 1/32	+	1 16	5		
	3/21/32	0	0 44	5	120	
8	4/11/32	0	0 25	60	172	
	4/19/32	0	0 3	0		
9	8/ 3/32	+	2 4	15	258	1 60
	8/14/32	+	3 6	55		
	8/19/32	+	1 84	30		
	8/21/32	0	1 04	15		
	8/24/32	0	1 04	5		1 10
10		0	0 43	10	147	
11	6/29/32	+	3 2	80	141	0
	7/ 5/32	0	1 08	0		
12	7/ 3/32	+	4 4	50	148	1 200
	7/14/32	0	0 64	5		
	7/20/32	0	0 53	0		
13		+	4 4	20	164	1 10
14		+	4 2	60		
15		+	2 48	20		
16	5/10/32	+	5 2	100	101	
	5/16/32	0	1 01	0		
17		0	1 4	50	106	
18		0	2 4	0	142	
19		0	1 0	100		
20		+	3 1	80	105	1 25
21		+	1 9	25		1 50
22		0	0 9	10	211	
23		+	3 1	5		
24		0	1 5	0	188	
25		+	3 1	60	122	1 40
26		+	1 8	10	158	
27		+	2 1	20		
28		0	0 88	5	186	
29		0	0 84	10	165	
30		0	1 1	5	168	
31		0	0 7	10	281	
32	1/18/33	+	4 0	100	181	1 150
	1/24/33	+	6 0	100		1 50
	2/ 1/33	+	1 87	40		
33		+	2 05	40		1 40
34		+	1 5	0		1 20
35		0	0 4	5	216	
36		+	2 3	10	195	1 10
37		0	0 8	10	104	1 10
38	3/28/33	0	0 52	30	253	1 20
	4/ 4/33	0	0 4	5		0
39		0	1 6	0		
40		0	1 1	0		
41		+	1 4	5	152	0
42		0	1 2	0		
43	5/31/33	+	17 1	100	112	0
	7/ 5/33	0	0 75	0		
44		+	4 25	100	226	1 10
45		+	2 5	70	94	
46		+	4 8	80	128	0
47	7/15/33	+	8 3	60		
	7/28/33	0	1 25	40	132	
	8/ 8/33	0	0 42	0		
48	7/26/33	0	1 1	50		1 40
	8/ 4/33	+	3 65	40		1 60
49		+	1 75	20		0
50		+	2 4	60	116	1 50
51		0	1 8	0		1 50
52		0	1 6	10	144	
53		+	2 4	60		1 80
54		+	2 6	40	182	
55		0	1 2	10	193	
56		+	3 1	80		1 60
57		0	1 1	10	164	
58		+	1 9	0		
59		+	2 3	20		
60		+	3 5	10		
61		0	0 8	40	172	
Cases		Serum Bilirubin	Bromsulphalein Retention	Plasma Cholesterol		Urobilinogen in the Urine
77		0 14 0 98	0	152 234		0 1 20

TABLE 7—Stone in the Common Bile Duct

Case	Date	Direct Van den Bergh	Serum Bilirubin	Brom sulphalein Retention	Plasma Cholesterol	Urobilinogen in the Urine
1		+	3 5	10		1 10
2	1/26/32	+	5 16	100	276	1 10
	2/ 8/32	+	22 8	90		
	2/15/32	+	13 2	60		
	2/27/32	+	5 7	80	200	
	3/ 9/32	+	1 3	30	250	
	3/15/32	0	1 12	10		1 60
3	2/27/32	+	41 6	100	366	0
	3/ 9/32	+	23 0	100	480	
	3/17/32	+	21 6	100	526	
	3/29/32	+	14 4	100	400	
	4/10/32	+	18 0	100	404	
	4/28/32	+	4 4	60	408	1 100
	5/ 8/32	+	4 4	90		
	5/15/32	+	1 5	80	200	
	5/22/32	+	5 6	80		
	5/29/32	+	1 3	15	388	
	5/30/32	+	1 26	0		1 80
	7/14/32	0	0 88	0	276	
4		0	0 6	80	242	
5	4/25/32	+	18 4	80	694	0
	5/ 1/32	+	13 0	60		
	5/ 8/32	+	2 03	0		
	5/15/32	0	2 1	0	288	1 60
	5/22/32	0	1 5	0	140	
6	5/ 8/32	+	19 0	100		1 10
	5/15/32	+	6 2	60	211	
	5/22/32	+	3 0	50		
	5/29/32	+	2 6	50	347	1 100
	6/ 6/32	0	1 0	10	258	
7		+	11 2	30	202	0
8	9/26/32	0	2 9	0	200	1 60
	10/ 5/32	0	1 28	0		
	10/14/32	0	0 81	10		
	10/16/32	+	13 8	80	244	0
9		+	26 0	100		
10		+	36 8	100		0
11		+	4 2	40		1 20
12	10/ 6/32	+	7 1	80		1 10
	10/15/32	+	9 3			
	10/20/32	+	6 8			
13		+	4 8	15	245	
14		+	11 2	100	206	0
15		+	8 1		184	0
16		+	7 5		209	0
17		+	6 0			
18		+	12 0	100		
19		+	5 32	80	186	1 10
20		+	6 0	70	224	
21	1/ 8/33	+	4 3	30		0
22	1/15/33	+	8 5	80		0
		+	7 5	40	241	
23	4/ 8/33	+	3 0	20	178	
	4/12/33	0	0 84	0		
24		+	10 0	80		
25	7/25/33	+	8 5	100	168	1 10
	7/29/33	+	6 5	80		
	8/ 2/33	+	5 8	65		
	8/15/33	+	3 0	15		1 50
26		+	3 9	60	168	
27		+	6 0	80	100	
28		+	13 3	100		
29		+	5 2	100		
30	6/23/33	+	11 0			0
	7/ 1/33	+	8 0	80		
	7/11/33	+	10 0	60		
	7/18/33	+	9 0	90		
	7/25/33	+	9 0	80		
	8/ 1/33	+	4 5	70		
31	6/20/33	+	12 0	100	210	1 10
	7/26/33	0	1 0	0	94	1 100
					126	1 20
Cases	Serum Bilirubin		Bromsulphalein Retention	Plasma Cholesterol		Urobilinogen in the Urine
6	0 64 0 98		0	169 192		1 10-1 20

Calculous Cholecystitis—Evidence suggestive of hepatic functional impairment was obtained in 61 of 138 cases (44.8 per cent) of calculous cholecystitis without stones in the common bile duct (table 6). Retention of bromsulphalein (from 5 to 100 per cent) was present in 52 cases, hyperbilirubinemia (from 1.1 to 17.1 mg), in 50, hypercholesteremia (from 211 to 281 mg), in 7, hypocholesteremia (from 93 to 132 mg), in 15, and urobilinuria (from 1.25 to 1.200), in 15 cases.

Stone in the Common Bile Duct—Abnormal findings were obtained in 31 (83.7 per cent) of 37 patients with stone in the common duct (table 7). Retention of bromsulphalein (from 10 to 100 per cent) was present in 28 cases, hyperbilirubinemia (from 1 to 26 mg), in 30, hypercholesteremia (from 202 to 694 mg), in 13, hypocholesteremia (from 94 to 100 mg), in 2, and urobilinuria (from 1.50 to 1.100), in 7 cases.

COMMENT

Noncalculous Cholecystitis—Obviously, because of the location of the pathologic lesion, hyperbilirubinemia cannot result from uncomplicated cholecystitis. The occurrence of this phenomenon in association with noncalculous cholecystitis is dependent on the development of one or more of several complicating factors, among which are cholangitis, pancreatitis, hepatitis, spasm of the hepatic or common ducts, enlargement of the lymph nodes and obstruction of the common duct by a plug of mucus or, rarely, a portion of a membranous cast of the gall-bladder. Although the majority of earlier observers stated that jaundice occurred only infrequently in patients with noncalculous cholecystitis, more recent studies, with the improved methods now available, have served to emphasize the rather high incidence of hyperbilirubinemia in this condition.

In a series of 375 patients with noncalculous cholecystitis, Hartman⁴ found jaundice in 60 cases, or 16 per cent, as compared with 31.74 per cent of a series of 652 patients with gallstones. Kelly and Lyon⁵ stated that jaundice may occur in 35.3 per cent of cases of cholecystitis in the absence of gallstones. The latter figure is considerably higher than that given by the majority of authors, but I believe that careful and repeated study of the serum bilirubin concentration will reveal a remarkably high incidence of hyperbilirubinemia, with or without visible jaundice, in patients with acute or chronic cholecystitis which is apparently, although not actually, uncomplicated. In the present series, hyper-

⁴ Hartman, H. R. Jaundice in Surgical Cholecystitis Without Stones, *M. Clin. North America* 7:89, 1923.

⁵ Kelly, A. O. J., and Lyon, B. B. V., in Osler and McCrae. *Modern Medicine*, ed. 3, Philadelphia, Lea & Febiger, 1926, vol. 3, p. 862.

bilirubinemia was present in 16.3 per cent of cases of acute, and in 15.2 per cent of cases of chronic, noncalculous cholecystitis.

Hepatitis, or intrahepatic cholangitis, is perhaps the most common cause of nonobstructive hyperbilirubinemia in patients with cholecystitis. The frequency of occurrence of this lesion is illustrated by the fact that Graham⁶ found enlargement of the liver in 25 (83 per cent) of 30 consecutive cases of disease of the biliary tract, evidence of previous or present disease other than enlargement being noted in the remainder. He stated that microscopic evidence of hepatic inflammation, chiefly pericholangitis, may be observed constantly in acute and subacute cholecystitis. Graham's interpretation of these observations has recently been challenged by Noble,⁷ who found similar changes almost constantly in livers examined post mortem. Noble stated that portal infiltration by lymphocytes and polymorphonuclear leukocytes seems to have no particular relation to a specific type of disease. He also stated, however, that since no cases of clinical cholecystitis were included in his series, no definite conclusion can be drawn concerning the degree of hepatic inflammation in clinical cholecystitis. This concept of the association between cholecystitis and hepatitis has been supported by the majority of investigators of this problem, including Judd,⁸ Deaver,⁹ Peterman, Priest and Graham,¹⁰ Moynihan¹¹ and Tietze and Winkler.¹² It is believed that whereas the hepatic lesion may be and unquestionably is in many instances secondary to the inflammatory process in the gallbladder, in many cases cholecystitis represents a direct extension of the process to the wall of the gallbladder from an already inflamed liver. In either event the extension occurs by way of the lymphatics.

In some cases, the hyperbilirubinemia is undoubtedly obstructive and is due to some obstruction of the free flow of bile through the common duct. In 6 of 7 cases of noncalculous cholecystitis reported by Eusterman,¹³ with an average serum bilirubin concentration of 8.1 mg, there

6 Graham, E. A. Hepatitis, a Constant Accompaniment of Cholecystitis, *Surg, Gynec & Obst* **26** 521, 1918.

7 Noble, J. F. The Relation of Hepatitis to Cholecystitis, *Am J Path* **9** 473, 1933.

8 Judd, E. S. Relation of the Liver and the Pancreas to Infection of the Gallbladder, *J A M A* **77** 197 (July 16) 1921.

9 Deaver, J. B. The Sequelae of Biliary Tract Infection, *J A M A* **95** 1641, 1930.

10 Peterman, M. G., Priest, W. S., Jr., and Graham, E. A. Association of Hepatitis with Experimental Cholecystitis, *Arch Surg* **2** 92 (Jan) 1921.

11 Moynihan, B. Mitchel Banks Memorial Lecture on the Gallbladder and Its Infections, *Brit M J* **1** 1, 1928.

12 Tietze, A., and Winkler, K. Die Beteiligung des Leberparenchyms an der Gallensteinkrankheit, *Arch f klin Chir* **129** 1, 1924.

13 Eusterman, G. B. Errors in the Diagnosis of Diseases Associated with Jaundice, *Ann Int Med* **6** 608, 1932.

was definite evidence of associated disease of the liver, pancreas or common duct Hartman⁴ reported the presence of pancreatitis in 26 per cent of 60 patients with jaundice associated with noncalculous cholecystitis Diamond¹⁴ obtained increased serum bilirubin values in 27 of 98 cases of cholecystitis, the highest being observed in acute cholecystitis (to 12 mg) Judd, Nickel and Wellbrock¹⁵ stated that hepatitis or cholangitis always occurred in the presence of cholecystitis, the importance of this association was emphasized by Judd and McIndoe,¹⁶ who stated that chronic cholangitis forms the etiologic basis of most microscopic lesions of the liver associated with infection of the gallbladder, and that this infection is more important than obstruction in producing severe hepatic injury Riedel¹⁷ and Naunyn¹⁸ emphasized the part played by cholangitis and spasm of the common duct in the production of jaundice in disease of the gallbladder Hyperbilirubinemia in acute forms of cholecystitis is more likely to be due to cholangitis or hepatitis and less likely to be dependent on pancreatitis than in chronic disease of the gallbladder, it occurs more frequently in the more severe than in the mild forms of acute cholecystitis, chiefly because of the higher incidence of hepatitis and cholangitis in the severe cases

The statement is frequently made that, except in portal cirrhosis, abnormal retention of bromsulphalein occurs only in the presence of hyperbilirubinemia On the basis of my observations in a large number of patients with noncalculous cholecystitis, I am convinced that the chief practical significance of the bromsulphalein test in such cases lies in the fact that abnormal findings are obtained in a not inconsiderable proportion of patients with acute and chronic cholecystitis without other demonstrable evidence of disturbed hepatic function This opinion was stated in a previous report¹ and has been strengthened by the data included in the present study I believe that the presence of retention of bromsulphalein of from 5 to 100 per cent in a group of 32 patients without hyperbilirubinemia is of extreme practical importance In my previous study there were 3 patients presenting 100 per cent retention of dye with icterus index values of 83, 72 and 87, respectively In the present group of patients with noncalculous cholecystitis, similar cases were observed serum bilirubin, 0.83 mg, and retention of dye, 80 per cent (table 2, case 2), serum bilirubin, 0.8 mg, and retention of dye, 100 per cent (case 11), serum bilirubin, 1.1 mg, and retention of

14 Diamond, J. S. The Value of Routine Estimations of Blood Bilirubin, *Am J M Sc* **176** 321, 1928

15 Judd, E. S., Nickel, A. C., and Wellbrock, W. L. A. The Association of the Liver in Disease of the Biliary Tract, *Surg, Gynec & Obst* **54** 13, 1932

16 Judd, E. S., and McIndoe, A. H. Cholangitis, *J Michigan State M Soc* **29** 174, 1930

17 Riedel. Ueber die Gallensteine, *Berl klin Wchnschr* **38** 1, 40 and 78, 1901

18 Naunyn, B. Cholelithiasis, *Tr New Sydenham Soc*, 1896, p 76

dye, 100 per cent (table 3, case 16) Such data appear to indicate that in certain cases with only slight if any impairment in the function of excreting bilirubin the capacity of the liver for eliminating bromsulphalein is greatly impaired These findings suggest dissociation of these two phases of the excretory function of the liver Such marked grades of retention of dye must be dependent on a widespread disturbance, involving a considerable portion of the liver, on the other hand, this disturbance is apparently readily amenable to correction, since essentially normal findings may be obtained within a short space of time following the institution of proper therapeutic procedures (table 2, case 11) These observations suggest that the hepatic disorder is largely functional, secondary to organic disease of the gallbladder or bile ducts and associated with only slight if any organic disease of the hepatic polygonal cells The presence of hepatic functional impairment in this group of patients is further evidenced by the observation of hypocholesteremia in 19 and urobilinuria in 20 cases The significance of hypocholesteremia in this connection has been emphasized by Epstein¹⁹

Cholelithiasis—It is obvious that stones in the gallbladder are not in themselves capable of producing jaundice However, as has been indicated earlier, disease of the gallbladder is frequently complicated by lesions which may cause hyperbilirubinemia Hartman⁴ found such lesions as hepatic cirrhosis, hepatitis, cholangitis, pancreatitis and mucous plugs in the common duct in a series of 166 patients with jaundice associated with stones in the gallbladder and not in the common duct Hepatitis was present in 16.9 per cent, cirrhosis in 5.31 per cent, cholangitis in 3.86 per cent, pancreatitis in 28.01 per cent, and enlarged lymph nodes around the bile ducts in 15.45 per cent Hartman stated the belief that pancreatitis is a common cause of jaundice in such cases Eusterman¹⁸ reported 85 cases of stones in the gallbladder with jaundice at the time they came under observation, the average serum bilirubin concentration being 7 mg He stated that gross evidence of changes in the liver, pancreas and extrahepatic bile ducts was noted at operation in 77 per cent of these cases According to Riedel,¹⁷ extension of spasm or inflammation from the cystic to the common duct is responsible for the occurrence of icterus in from 10 to 15 per cent, and, according to Naunyn,¹⁸ in 40 per cent of cases in which a stone is implanted at the neck of the gallbladder or in the cystic duct

In the present series of 138 patients with calculous cholecystitis, hyperbilirubinemia was present in 36.2 per cent of cases Some degree of retention of bromsulphalein was present at some time in 37.6 per cent of these patients As in the group of persons with noncalculous

¹⁹ Epstein, E. Z. Cholesterol of the Blood Plasma in Hepatic and Biliary Diseases, *Arch Int Med* 50:203 (Aug.) 1932

cholecystitis, a marked disproportion between the degree of retention of bromsulphalein and of bilirubinemia was noted in several instances. This, with the not infrequent occurrence of hypocholesteremia and urobilinuria, is in my opinion highly suggestive of the fact that hepatic functional impairment is a not uncommon complication of calculous cholecystitis in the absence of clinical jaundice or, at times, hyperbilirubinemia. The aforementioned statements in connection with non-calculous cholecystitis are equally applicable here.

Naturally, because of the possibility of effectively obstructing the outflow of bile, stones in the common duct are more likely to produce hyperbilirubinemia than are stones in other portions of the bile passages. According to Kehr,²⁰ about 75 per cent of all patients with stones in the common bile duct have jaundice at some time. In a series of 1,608 cases, Judd and Marshall²¹ obtained a history of jaundice in 73.4 per cent, icterus being present at the time of admission in 18.8 per cent of the patients. Jordan²² and Weir²³ stated that about 13 per cent of persons with stone in the common bile duct exhibited no jaundice at any time. Moynihan²⁴ stated that jaundice is absent in 25 per cent of these cases. Some degree of cholangitis, hepatitis, cholecystitis and pancreatitis is commonly present in association with stone in the common duct. Kehr²⁰ and Riedel¹⁷ minimized the mechanical rôle of the stone and emphasized the inflammatory reaction in the duct mucosa as the cause of jaundice, Riedel stating that the latter factor is operative in 40 per cent of cases.

Hyperbilirubinemia was present in 81 per cent of 37 patients in this series with stone in the common duct. Some degree of retention of dye was present in 75.6 per cent of these cases. Obviously, little if any information can be gained from studies of the retention of bromsulphalein during periods of obstructive jaundice. However, as may be noted in cases 2, 3 and 6 (table 7), the speed of restoration of the capacity of the liver for eliminating bromsulphalein does not always parallel the decrease in the degree of bilirubinemia which follows spontaneous resumption of the flow of bile. Case 4 illustrates the existence of marked retention of dye in the absence of hyperbilirubinemia.

It has been my experience, as is illustrated by several cases included in this report, that the routine study of the state of hepatic function

20 Kehr, H. *Chirurgie der Gallenwege*, Berlin, Ferdinand Enke, 1913.

21 Judd, E. S., and Marshall, J. M. Gallstones in the Common Bile Duct, *Arch Surg* **23** 175 (Aug.) 1931.

22 Jordan, F. M. Stones in the Common Bile Duct Without Jaundice, *Proc Staff Meet., Mayo Clin* **5** 56, 1930.

23 Weir, J. F. Diagnosis of Jaundice. Value of Clinical and Laboratory Data, *Am J Surg* **15** 494, 1932.

24 Moynihan, B. The Correlation of Symptoms and Signs in Some Abdominal Diseases, *Brit M J* **1** 345, 1912.

in all patients with calculous and noncalculous cholecystitis, so far as it can be studied, frequently yields information of distinct practical value. The presence of retention of bromsulphalein is particularly significant in the absence of or during the disappearance of obstructive jaundice. On the basis of the data presented, three points deserve special emphasis, (1) that some evidence of disturbed hepatic function can be obtained in a fairly large proportion of cases of calculous and noncalculous cholecystitis, (2) that marked grades of retention of bromsulphalein may occur in patients with disease of the biliary tract in the absence of hyperbilirubinemia, (3) that in certain cases of stone in the common duct, some degree of retention of dye persists for a variable period after a previously high serum bilirubin concentration has returned to normal. In my opinion, appreciation of these facts will do much to diminish the postoperative morbidity and mortality of operations on the biliary tract.

SUMMARY

1 In a group of 49 patients with acute cholecystitis, hyperbilirubinemia was present at some time in 8 cases, retention of bromsulphalein in 11, hypercholesteremia in 2, hypocholesteremia in 4, and urobilinuria in 4.

2 Some evidence suggestive of hepatic functional impairment was noted in 76 (26.3 per cent) of 288 patients with chronic noncalculous cholecystitis. Retention of bromsulphalein without hyperbilirubinemia was noted in 32 cases, hyperbilirubinemia and retention of dye in 29 and hyperbilirubinemia without retention of dye in 15. Hypercholesteremia was present in 4 cases, hypocholesteremia in 15 and urobilinuria in 16.

3 Evidence suggestive of hepatic functional impairment was obtained in 61 (44.8 per cent) of 138 patients with calculous cholecystitis. Retention of dye was present in 52 cases, hyperbilirubinemia in 50, hypercholesteremia in 7, hypocholesteremia in 15 and urobilinuria in 15.

4 Abnormal findings were obtained in 31 (83.7 per cent) of 37 patients with stone in the common bile duct. In some cases it was noted that the speed of restoration of the capacity of the liver for eliminating bromsulphalein did not parallel the decrease in the degree of bilirubinemia which follows spontaneous resumption of the flow of bile.

5 The data reported illustrate the frequency of occurrence of hepatic functional impairment in apparently uncomplicated disease of the gall-bladder. Retention of bromsulphalein of marked degree may exist in the absence of hyperbilirubinemia.

PUTRID EMPYEMA

WITH SPECIAL REFERENCE TO ANAEROBIC STREPTOCOCCI

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Cases of abscess of the lung, pulmonary gangrene, bronchiectasis and certain types of bronchopneumonia are occasionally complicated by the development of pleural effusion. When the pleural fluid is aspirated, it is frequently found to be purulent and to have a foul odor. It is because of this characteristic odor that a pleural effusion of this type is termed putrid empyema. Occasionally this fluid is thin, but more often it is moderately thick and of creamy consistency. It may be yellowish-green or brown, depending on the amount of fresh or changed blood present. In spite of the fact that microscopic examination of the putrid exudates often reveals the presence of many micro-organisms, attempts to cultivate the bacteria under ordinary aerobic conditions may prove unsuccessful. However, the use of anaerobiosis often yields an abundant growth of one or more kinds of bacteria.

The purpose of this article is to report the bacteriologic observations and clinical course in 7 cases of severe purulent infections and to emphasize the occurrence and probable importance of anaerobic streptococci in the pathogenesis of the diseases from which the patients suffered. Four of the patients had putrid empyema, 2 had pulmonary abscess, and 1 had multiple hepatic abscesses. The cases of empyema were studied in more detail than the others. Consequently, the clinical and bacteriologic observations of these cases are given special consideration in this communication.

REVIEW OF THE LITERATURE

A review of the literature dealing with putrid, purulent infections reveals a diversity and complexity of bacteriologic results, and each author stresses the importance of a different organism or combination of organisms. The association of anaerobes, including anaerobic streptococci, with putrid empyema has been recognized for many years, and organisms of similar types are also found in various other pathologic states, such as pulmonary abscess and gangrene, puerperal infections

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and mastoiditis. An attempt is made here to summarize the literature dealing with putrid empyema and also that dealing with infections in which the anaerobic streptococcus is found. Thus it may be possible to throw some light on the significance of this type of organism and to gain some insight into its importance in certain infections.

Lesions in Which Anaerobic Streptococci Are Found—The occurrence of an anaerobic streptococcus in pathologic lesions was first mentioned by Veillon,¹ in 1893, who isolated it from a case of Bartholinitis. The pus had a foul odor, as did the culture of the coccus and the pus from an abscess produced by subcutaneous injection of the organism into an animal. Veillon also found the organism in the fetid pus from a case of Ludwig's angina and from a perinephric abscess, but in the latter cases it was in association with a pyogenic streptococcus. Two years later Kronig² described the occurrence of an anaerobic streptococcus, sometimes alone and sometimes with anaerobic bacilli, in the vaginal secretion during pregnancy. The streptococcus was found to be avirulent for rabbits. Since the reports of these earlier workers, the studies of many authors up to the present time have indicated the widespread occurrence of the anaerobic streptococcus in many and varied lesions. A review of the literature shows that it may be found under a great variety of conditions, but the two types of infections in which it seems to play its most important rôles are (1) putrid or gangrenous lesions of the lung or pleura and (2) puerperal infections with or without sepsis.

In Putrid Empyemas (and Pulmonary Lesions) The majority of the authors who have studied the subject of putrid pleurisy have found that the pus from these lesions contains an anaerobic streptococcus. This organism is nearly always associated with other bacteria, however, especially with anaerobic bacilli, fusiform bacilli and spirochetes. In 1899, anaerobic streptococci and gram-negative bacilli were found by Rendu and Rist³ in 3 cases of putrid pleurisy. Guillemot, Hallé and Rist⁴ found the organism (as well as anaerobic bacilli and aerobic streptococci) in the majority of 13 cases of putrid empyema. In 1921,

1 Veillon, A. Sur un microcoque anaérobe trouvé dans des suppurations fétides, *Compt rend Soc de biol* **5** 807, 1893.

2 Kronig. Ueber die Natur der Scheidenkeime, speciell über das Vorkommen anaerober Streptokokken im Scheidensekret Schwangerer, *Centralbl f Gynak* **19** 409, 1895.

3 Rendu and Rist, E. Etude clinique et bactériologique de trois cas de pleurésie putride, *Bull et mém Soc med d hôp de Paris* **16** 133, 1899.

4 Guillemot, L. Hallé, J., and Rist, E. Recherches bactériologiques et expérimentales sur les pleuresies putrides, *Arch de med exper et d'anat path* **16** 57 and 677, 1904.

Bingold⁵ stressed the formation of gangrenous or fetid pulmonary and pleural lesions as a result of emboli containing the anaerobic streptococcus lodging in the lungs in the course of thrombophlebitic puerperal sepsis. In these cases the organism can be obtained from the pelvic veins, the blood stream and the pulmonary lesions. Bingold concluded that the chief cause of embolic pulmonary gangrene is the anaerobic streptococcus. Davis and Pilot⁶ found it with a fusiform bacillus and spirochete in 4 cases of putrid pneumonia and were able to culture it and the fusiform bacillus from the empyema fluid which developed in 1 of the cases. Similar bacteriologic observations were reported by Leckie⁷ in 1 case of putrid empyema. Eggers⁸ found streptococci, some of which were apparently anaerobic, in several cases of empyema secondary to pulmonary abscesses. Anaerobic cocci, bacilli and spirochetes were found in the putrid pleural fluid of a patient by Bezançon and his co-workers⁹ and later in another case by Jacquelin, Brun and Fouquet¹⁰. Brown¹¹ and Colebrook,¹² who were studying the relation of the anaerobic streptococcus to puerperal infection each had a case in which it could be grown from the pleural fluid as well as from the blood. Pilot¹³ reported a case of putrid empyema in which streptococci and fusiform bacilli were found in the stained smear of the fluid, while culture revealed only an anaerobic streptococcus.

A summary of the bacteriologic reports on approximately 26 cases of putrid empyema collected from the literature shows that the anaerobic streptococcus was found in 13 (probably also in 4 others in which strep-

5 Bingold, K. Putride embolische Lungeninfektionen, Aetiologie und Pathologie, *Virchows Arch f path Anat* **232** 22, 1921, Die Bedeutung anaerober Bacterien als Infektionserreger septischer interner Erkrankungen, *ibid* **234** 333, 1921.

6 Davis, D. J., and Pilot, I. Studies of *Bacillus Fusiformis* and Vincent's Spirochete, Habitat and Distribution of these Organisms in Relation to Putrid and Gangrenous Processes, *J A M A* **79** 944 (Sept 16) 1922.

7 Leckie, J. P. Fatal Case of Empyema Due to Anaerobic Infection, *Edinburgh M J* **30** 60 (Feb) 1923.

8 Eggers, C. Lung Abscess Complicated and Hidden by Empyema, *Arch Surg* **12** 338 (Jan) 1926.

9 Bezançon, F., and others. Sur la presence de spirochaetes associes aux anaerobes dans un cas de pleuresie putride, *Bull et mem Soc med d hôp de Paris* **51** 1153 (July 14) 1927.

10 Jacquelin, A., Brun, C., and Fouquet. Sur un cas de pleurésie putride cause par la flore spirocheto-anaerobe, *Bull et mem Soc med d hôp de Paris* **53** 1219 (Nov) 1929.

11 Brown, T. K. The Incidence of Puerperal Infection Due to Anaerobic Streptococci, *Am J Obst & Gynec* **20** 300 (Sept) 1930.

12 Colebrook, L. Infection by Anaerobic Streptococci in Puerperal Fever, *Brit M J* **2** 134 (July 26) 1930.

13 Pilot, I. Putrid Empyema as a Postoperative Complication, *M Clin North America* **13** 1227 (March) 1930.

tococci were found in a smear of the fluid, although no growth was obtained), gram-negative bacilli in 5 or 6, gram-positive bacilli in at least 2, fusiform bacilli in 5, spirochetes in 5, anaerobic staphylococci in 4, aerobic *Staphylococcus aureus* in 1 and aerobic streptococci in 2. This summary by no means contains all of the cases of putrid pleurisy which have been reported, but in others the bacteriologic studies are not so definite as the aforementioned, and these give a general idea of the organisms most often found.

Inasmuch as putrid empyemas are rarely, if ever, primary but practically always secondary to intrapulmonary suppuration or necrosis, it is not surprising that the anaerobic streptococcus is being found frequently in the primary or pulmonary as well as in the secondary or pleural lesions. Various authors have cultured the anaerobic streptococci from putrid pulmonary infections such as abscess, gangrene and bronchiectasis. The observations of Bingold have been mentioned earlier, Lehmann, too, pointed out the nearly constant occurrence of putrid lung pulmonary abscesses in the course of puerperal sepsis due to the anaerobic streptococcus. In addition, there are the reports of Davis and Pilot,¹⁴ who found a streptococcus which was "often anaerobic in early cultures," in cases of putrid pneumonia, pulmonary abscess and gangrene (in association with spirochetes and fusiform bacilli), Lambert and Miller¹⁵ grew it from 6 of 10 cases of pulmonary abscess (an anaerobic gram-negative bacillus was found in 7), Smith¹⁶ found only anaerobes in the pus from 3 cases of pulmonary abscess—cocci, vibrios, fusiform bacilli and spirochetes—and the same organisms were shown in sections of the ulcerated bronchi in acute cases. Ermatinger¹⁷ isolated facultatively anaerobic streptococci in some cases of pulmonary abscess and bronchiectasis. Cohen¹⁸ cultured an anaerobic streptococcus from the pus in each of 16 cases of pulmonary abscess, in all of these there was also a diphtheroid bacillus, and in 14 of the 16 there was a strictly anaerobic gram-negative bacillus (*Bacillus melaninogenicum*, an organism producing black pigment and a fetid odor on blood agar). The streptococcus was nonhemolytic and was called a "doubtful" anaerobe.

14 Pilot, I, and Davis, D. J. Studies in Fusiform Bacilli and Spirochetes Their Rôle in Pulmonary Abscess, Gangrene and Bronchiectasis, *Arch. Int. Med.* **34** 313 (Sept.) 1924. Davis and Pilot.⁶

15 Lambert, A. V. S., and Miller, J. A. Abscess of Lung, *Arch. Surg.* **8** 446 (Jan.) 1924.

16 Smith, D. T. Fusio-Spirochetal Disease of the Lungs, *Tubercle* **9** 420 (Nov.) 1927.

17 Ermatinger, L. H. Micro-Organisms of Lung Abscess and Bronchiectasis, *J. Infect. Dis.* **43** 391 (Nov.) 1928.

18 Cohen, J. Bacteriology of Abscess of Lung and Methods for Its Study, *Arch. Surg.* **24** 171 (Feb.) 1932.

because it was found to grow aerobically on subcultures though not on the original one

In Puerperal and Pelvic Infections In 1910 Schottmuller¹⁹ found the anaerobic streptococcus in 17 cases of septic abortion, in 5 he obtained it in pure culture from the blood (He also cultured it in 2 cases of otitis media and in 1 case of pulmonary gangrene) In cases of puerperal sepsis or septic abortion due to this organism, these infections are usually associated with pelvic thrombophlebitis, and Schottmuller stated the belief that the streptococci are able to "dissolve the thrombi" so that small particles break off In 1924²⁰ he cultured the anaerobic streptococcus from the blood and peritoneal exudate during life in 39 of 230 fatal cases of sepsis following labor Many other authors have shown the importance of this organism in puerperal infection, and their studies indicate that it is not only commonly found under these conditions, but that its pathogenicity is comparable to that of the aerobic hemolytic streptococcus Bingold⁵ discussed the importance of the anaerobic streptococcus in various infections, especially in puerperal fever with thrombophlebitis He had seen 60 cases of sepsis due to this organism, in all of which pulmonary abscess or gangrene developed, he stated that the fatal outcome of cases of sepsis due to an anaerobic streptococcus is often due to the pulmonary complications Three of the patients had purulent meningitis, and 3 had endocarditis Lehmann²¹ also reported 3 cases of endocarditis due to this streptococcus, associated with septic abortion and bacteremia (In neither of these cases was there a history of previous rheumatism or of old endocarditis histologically) Lehmann found it to be the single infecting agent in 17 of 27 cases of sepsis with thrombophlebitis, in 8 of 12 cases of pelvic abscess and in many cases of salpingitis Schwarz and Dieckmann²² cultured the streptococcus from the blood in 30 of 123 cases of puerperal infection, and later²³ from the blood in 10 of 45 cases Harris and Brown²⁴ found it with approximately the same frequency as the aerobic

19 Schottmuller, H Zur Bedeutung einiger Anaeroben in der Pathologie insbesondere bei puerperalen Erkrankungen, *Mitt a d Grenzgeb d Med u Chir* **21** 450, 1910

20 Schottmuller, H Ueber die Artverschiedenheit der Streptokokken, *Munchen med Wchnschr* **71** 1009, 1924

21 Lehmann, W Die Bedeutung anaerober Streptokokken fur die Aetologie der akuten septischen Endokarditis, *Munchen med Wchnschr* **73** 233, 1926

22 Schwarz, O H, and Dieckmann, W J Anaerobic Streptococci Their Role in Puerperal Infection, *South M J* **19** 470 (June) 1926

23 Schwarz, O H, and Dieckmann, W J Puerperal Infection Due to Anaerobic Streptococci, *Am J Obst & Gynec* **13** 467, 1927

24 Harris, J W, and Brown, J H A Clinical and Bacteriological Study of 113 Cases of Streptococcic Puerperal Infection, *Bull Johns Hopkins Hosp* **44** 1 (Jan) 1929

hemolytic streptococcus in 113 cases of puerperal infection. The majority of these streptococci were of the gamma nonhemolytic variety, and many of them failed to ferment the test sugars. Brown¹¹ found that this streptococcus was the infecting agent in a little more than half of 203 cases of puerperal infection. Colebrook¹² isolated the anaerobic streptococcus from the blood of 17 patients with puerperal fever, 7 of whom died and 1 of whom had "terminal" endocarditis.

The anaerobic streptococcus is also found in many other pathologic processes throughout the body, as may be shown by a glance at the literature. In 1898 Veillon and Zuber²⁵ found it in cases of gangrenous appendicitis and in a case of mastoiditis with pulmonary gangrene. In 1905 Rist²⁶ reported its isolation from cases of appendicitis, puerperal infection, Bartholin's infection, infection of the urinary tract, otitis media and mastoiditis. Lehmann²¹ stated that the organism sometimes produces foul-smelling tonsillar abscesses, and that it may be found in cases of appendicitis, frequently in mixed infections of the deep portion of the bronchial tree, in diseases of the ear, and in Vincent's angina, putrid alveolar abscesses and the like.

A classification of the strains of this streptococcus was given by Prévot²⁷ in 1925. He described six strains: 1. *Micrococcus foetidus* (Veillon, 1893), a strict anaerobe, produces gas and a foul odor and ferments saccharose but not lactose, maltose or mannite. 2. *Streptococcus anaerobius* (König, 1895, Natvig, 1905) is found especially in puerperal sepsis and is a strict anaerobe. One strain ferments saccharose and maltose, the other, maltose and mannite, producing gas and odor. 3. *Streptococcus putridus* (Schottmüller), a strict anaerobe, produces gas and odor. Maltose is fermented and occasionally saccharose and mannite. 4. *Streptococcus anaerobius-micros* (Lewkowicz, 1901) produces no gas or odor and no coagulation of milk or fermentation of saccharose and maltose. 5. *Streptococcus intermedius*, a strict anaerobe, is found in pulmonary conditions. It forms gas with a foul odor, coagulates milk with the production of acid and ferments maltose, lactose and, occasionally, saccharose. 6. Streptococci which are "anaerobes by predilection" show growth in the air, though it is slow and poor. Fourteen strains are reported, eleven of which are from pulmonary conditions. At first the organism is a strict anaerobe, but later it grows also aerobically, though not nearly so well. Gas and a foul odor are not produced in culture mediums. Milk is coagulated and acidified. Saccharose, mal-

25 Veillon and Zuber. Recherches sur quelques microbes strictement anaerobes et leur rôle en pathologie, Arch de méd exper et d'anat path **10**:517, 1898.

26 Rist, E. Anaerobes pathogènes et suppurations gangréneuses, Bull Inst Pasteur **3**: 1 and 49, 1905.

27 Prévot, A. R. Les streptocoques anaerobes, Ann Inst Pasteur **39**: 417, 1925.

tose and lactose are fermented. Prévot called this streptococcus *Streptococcus evolutus*. (He remarked that these anaerobic streptococci "live as saprophytes in the natural cavities and can become pathogenic when the opportunity offers".)

Pathogenicity for Animals—From the review of the literature just presented, it is evident that the majority of the reports dealing with the anaerobic streptococcus lead one to the conclusion that, at least under certain conditions, it is a truly pathogenic organism, in spite of the fact that it is frequently spoken of as a saprophyte of minor importance. The reports of experimental studies with this streptococcus are not extensive, and though some investigators show that it is pathogenic for animals when in association with other anaerobes, few have shown that pure cultures of the organism are capable of producing lesions in animals. Veillon¹ produced foul-smelling, subcutaneous abscesses with cultures of an anaerobic streptococcus (*M. foetidus*). The anaerobes isolated by Guillemot and his co-workers⁴ (*M. foetidus*, *Staphylococcus parvulus*, *Bacillus ramosus* and others) caused putrid lesions in rabbits and guinea-pigs when the original pus was injected. In this way, putrid pleurisy could be passed on from animal to animal, but none of the bacteria in pure culture were pathogenic. In 1905 Rist²⁶ found that anaerobes (bacilli and cocci) which he had isolated from various putrid lesions were pathogenic for animals when injected subcutaneously intrapleurally or intracutaneously. Pilot and Davis¹⁴ produced putrid empyemas in rabbits by intrapleural injections of tooth scrapings and tonsillar debris. The material that was injected, as well as the pus from the pleural cavity, contained spirochetes, fusiform bacilli and cocci. The cocci, when injected in pure culture, produced serofibrinopurulent pleuritis but no odor. In 1930 Smith²⁸ showed that putrid pulmonary infections or subcutaneous abscess could be produced in rabbits by intratracheal or subcutaneous injections of mixtures of pure cultures of *Treponema microdentium*, a small fusiform bacillus, a vibrio and an anaerobic hemolytic streptococcus. No strain by itself and no other combination could form lesions.

Some authors have definitely stated that they did not find the anaerobic streptococcus pathogenic for animals (Kronig,² Guillemot and others,⁴ Schottmuller¹⁹ and Lehmann²¹). Schottmuller employed cultures of an anaerobic streptococcus isolated from cases of pelvic infection and injected them into rabbits and guinea-pigs without producing any ill effects. The rabbits received intravenous, intramuscular and subcutaneous injections, and the guinea-pigs, intraperitoneal and subcutaneous injections. Cohen¹⁸ found that the doubtful anaerobic strep-

28 Smith, D. T. Fusospirochetal Disease of the Lung Produced with Cultures from Vincent's Angina, *J. Infect. Dis.* **46**: 303 (April) 1930.

tococcus which he obtained from pulmonary abscesses was not pathogenic for rabbits or guinea-pigs after intravenous or intracutaneous inoculation

Summary—Thus from the literature one gathers that the anaerobic streptococcus is an organism which may be found in a variety of pathologic conditions—especially those of a putrid or gangrenous nature—throughout the body. The lesions in which it seems to play its most important rôles are suppurations in the lung or pleural cavity and puerperal or other pelvic infections. The evidence points to the fact that it is definitely pathogenic for man, this is particularly convincing in cases of puerperal sepsis, when it can be obtained in pure culture from the pelvic veins, the blood and pulmonary abscesses, in these cases it likewise occasionally produces endocarditis. The experimental work is not conclusive, two authors obtained lesions in animals with this organism, while others have found that pure cultures of the anaerobic streptococcus are avirulent for animals, whereas with cultures in combination with other anaerobes the lesions can often be produced.

REPORT OF CASES

The 4 cases of putrid empyema included in this report were associated with an anaerobic streptococcic infection. In 1 case, which will be reported in detail, the organism (an anaerobic streptococcus) was the principal factor in the production of the patient's pneumonia, with resultant pulmonary abscess, empyema, metastatic abscesses in the skin and bones, endocarditis and eventual death. In 3 other cases it was the most conspicuous organism present, although associated with other anaerobes. In 2 cases it was obtained from pulmonary abscesses at operation. In 1 rather obscure case of unexplained fever it was responsible for the production of multiple hepatic abscesses.

CASE 1—History—F. B., aged 26, a colored laborer, married, was admitted to the hospital on Jan. 20, 1932, and died on March 14. The chief complaints were sore throat and great weakness of two weeks' duration. The family history was noncontributory. The general health had been good. The patient had had a primary syphilitic lesion five years before admission, which was inadequately treated by his family physician. For eight or ten years he had been troubled with an occasional dry cough and infrequent sweats at night, there had been no thoracic pain, dyspnea or hemoptyses. The patient had done the heavy work of a laborer prior to his admission to the hospital.

Sixteen days before admission he caught a cold following exposure to wet weather. Three days later a sore throat with pain on swallowing developed. Two days later the patient came to the hospital, where his temperature was found to be 101.6 F., the tonsils were red and covered with exudate. He was given sodium perborate as a gargle. He reported in the outpatient department the next day. The throat appeared to be unchanged, but the temperature had risen to 102 F., accompanied by a chill. He was advised to go home to bed and force fluids.

The Wassermann reaction was strongly positive. He returned to the outpatient department four days later, feeling much weaker and sick. During the next five days at home he became much worse, he was hoarse and had several chills followed by profuse sweats. One week prior to admission, he had a cough and blood-streaked sputum. He grew short of breath, and noticed pain in the left shoulder and right buttock. A sharp pain across the front of his chest when he coughed brought him into the hospital.

Physical Examination—The temperature was 103.8 F, the pulse rate, 140, the respirations, 42, and the blood pressure, 106 systolic and 64 diastolic. The positive findings were as follows. The patient was an emaciated, acutely ill colored man. The skin was hot and moist, and the forehead covered with perspiration. The conjunctivae were pale. The pupils were irregular and reacted sluggishly to light. Examination of the throat and mouth showed that the tongue was heavily coated, there was much sordes over the lips, pyorrhea was marked and the tonsils were enlarged and covered with exudate. The voice was hoarse. The trachea was in the midline. Respirations were shallow and rapid. There was dulness in the right axilla and interscapular region, with marked suppression of the breath sounds and many moist râles. Bronchovesicular breathing was heard in the right posterior axillary line. The left lung was clear. The heart was not enlarged. It was thought to be slightly displaced to the left. The rate was rapid and regular. The sounds were of good quality. No murmurs were heard. The peripheral vessels seemed normal, and the pulse was of good quality. The abdomen was somewhat distended but not tender. The liver and spleen were not felt. There was neither clubbing of the fingers nor edema of the extremities. The patient complained of pain in the right hip, but examination did not disclose any cause for this. There was tenderness about the left shoulder joint with pain on motion, but no swelling.

Examination of the Blood—The red blood cells numbered 3,300,000. The hemoglobin was 72 per cent, and the white cells 16,000, with 90 per cent polymorphonuclear leukocytes. The red cells were slightly pale, the platelets were normal in number. The urine showed specific gravity, 1.020, albumin, 2 plus, sugar, 0, many granular casts, white blood cells and occasional red blood cells. Culture of the throat produced *Staphylococcus aureus* and diphtheroids.

Course in the Hospital—The physical signs in the chest were suggestive of a pleural effusion, and thoracentesis was done on the evening of admission. The needle was inserted in several places over the right lower region of the chest posteriorly, in the region of the midaxillary line. Seventy-five cubic centimeters of fluid was withdrawn. It was foul-smelling, thin and reddish brown. A smear of the fluid showed a predominance of gram-positive cocci, mixed with gram-negative bacilli, fusiform bacilli and spirochetes. A smear from the throat showed a few spirochetes. The empyema was thought to have resulted from the rupture of a pulmonary abscess. The temperature rose to 105.6 F, and the condition became worse. A thoracotomy was done that night, and a trocar inserted in the seventh interspace in the midaxillary line. A rubber catheter was left in place and drainage instituted by means of continuous tidal irrigation (described by Hart). One hundred cubic centimeters of brownish foul pus was evacuated at the time of operation.

A blood culture taken on admission showed no growth aerobically. However, an anaerobic streptococcus was grown on cooked meat medium under a seal.

The patient was given fluids by mouth and subcutaneously in the thigh. Following a transfusion the next day he showed definite improvement. During the next

week the temperature varied between 101 and 105 F, accompanied by profuse sweats. There was a slight cough but no sputum. The patient had frequent chills. On the eighth day after admission the red blood cells had fallen to 2,500,000, and the hemoglobin to 50 per cent. The patient was given another transfusion with temporary improvement. The urine continued to show a moderate amount of albumin, a few red cells and white cells and few casts. Roentgenograms of the chest showed a "small area of partial consolidation in the lower lobe of the right lung." Physical examination revealed only a small amount of fluid in the right side of the chest.

On the tenth day after admission a firm swelling was noticed above the left clavicle at the acromial junction. This was quite tender. No evidence of osteomyelitis could be determined by roentgenograms, but a dense shadow was present in the soft tissues above the left clavicle. This area was treated with compresses. The temperature continued to vary daily from 100 to 104 F, the pulse rate between 110 and 140 and the respirations from 40 to 50. Frequent chills continued. The patient next had tenderness and induration over the right hip, with crepitation on palpation. A roentgenogram showed that there was air in the soft tissues. Blood culture taken on January 28 (the eighth day after admission) again yielded anaerobic streptococci. The signs over the lung changed little. The apparatus for irrigation often became obstructed, and drainage was not free. There were progressive anemia and leukocytosis.

On February 5, fifteen days after admission, a large abscess on the right heel was opened, and 75 cc of foul-smelling pus was obtained. This pus had the same odor as that obtained from the pleural cavity, smears of this fluid showed only a gram-positive coccus which on culture proved to be the same anaerobic streptococcus. Pus was also obtained from a similar area on the left heel. On the same day an incision was made into the area of swelling about the left clavicle, and 50 cc of pus of a similar character was obtained. Smears and culture showed the same organism. Sputum was obtained on several occasions. It did not show tubercle bacilli, hemolytic aerobic streptococci predominated. The improvement following the drainage of these areas was only temporary, the next day another abscess on the left buttock was drained, and a large amount of the same foul pus was obtained. Subsequently, the right knee was incised with the same results.

It was noted that each abscess contained much air, as well as thick, creamy, foul-smelling pus. The empyema irrigation system was also continually full of air, suggesting either a bronchial fistula or the production of air by the streptococcus. A roentgenogram of the left clavicle showed osteomyelitis of its outer end. The patient's condition grew progressively worse, in spite of repeated transfusions and apparently adequate drainage from numerous areas of abscess over the body. Repeated examinations of the heart revealed nothing that was not consistent with the anemia. The patient died on March 14, fifty-two days after admission and approximately sixty-six days from the onset of illness.

Autopsy—Autopsy was performed on March 15, 1932. The anatomic diagnosis was abscesses in the right lung, bronchial fistulas, organizing pneumonia, organizing fibrinopurulent pleurisy, purulent bronchitis, lobular pneumonia, septicemia (an anaerobic streptococcus), streptococcic endocarditis of the mitral valve, scars in the myocardium, osteomyelitis of the left clavicle, purulent arthritis of the right knee joint, multiple draining subcutaneous sinuses, acute nephritis, hypoplasia of the bone marrow, secondary anemia, hemosiderin in the liver and spleen and a decubitus ulcer.

A summary of the important gross and microscopic pathologic observations follows. The heart valves were thin and delicate, but there were several friable, gray-pink vegetations on the mitral valve. There were several abscess cavities of various sizes in the right lung, which communicated with one another by small openings, one of which extended to the pleural cavity. One cavity in the right lower lobe also communicated with a bronchus and with the operative wound in the chest to produce a bronchial fistula. A fibrinopurulent exudate was found in the right knee joint, with extensive destruction of the cartilage. There was extensive osteomyelitis of the left clavicle. The kidneys showed numerous punctate hemorrhages. The other organs were grossly normal.

Microscopically, one of the large cavities in the lung showed a communication with a bronchus, and the wall of the cavity was lined by granulation tissue, but there were areas suggesting smooth muscle in the wall of the cavity, probably representing a bronchiectatic dilatation of the chronically infected bronchus. However, there were fresh abscesses in the pulmonary substance. In the pleura there was a thick layer of granulation tissue with a more superficial, fresh fibrinopurulent exudate. All of these infections were apparently caused by an anaerobic streptococcus. No spirochetes were found. The vegetations on the mitral valve contained numerous colonies of bacteria, the vegetations were partly organized. The kidneys showed numerous hemorrhages with blood in the tubules. The bone marrow of the femur was gelatinous in appearance, and most of the myeloid cells had disappeared. The rest of the organs were normal.

Laboratory Studies—The original pleural fluid was thin and reddish brown and had a foul odor. A smear made from the fluid showed spirochetes, fusiform bacilli, many gram-positive cocci and gram-negative bacilli. There was no growth of the first culture aerobically on blood agar or in beef infusion broth. Another culture of the pus on blood agar aerobically showed, after five days, a few fine colonies of cocci which seemed to be just under the surface and were difficult to scrape off. Another sample of the pus put into a broth tube (aerobically) produced a slight granular growth at the bottom of the tube. Cultured anaerobically on cooked meat medium beneath a petrolatum seal, there were a granular growth and the production of gas with a foul odor. A stained smear of this culture showed only gram-positive cocci in short chains, singly and in pairs. A culture of the pleural pus on blood agar in an anaerobe jar showed a growth of small colonies of streptococci with a narrow zone of complete hemolysis. The other bacteria which were seen in smears of this pus grew neither aerobically nor anaerobically. In milk medium under petrolatum there was rapid growth, with the production of much acid, clotting and an offensive odor. In sugar mediums beneath petrolatum there was fermentation of sucrose, dextrose, maltose and lactose, but none of mannite. Anaerobic growth in broth produced only a slight odor. Transfer of the culture from the cooked meat medium to blood agar showed slow, fine growth aerobically after from five to eight days, and in an anaerobe jar on blood agar, good growth in two days with moderately intense but complete hemolysis.

Experiments in Animals (Brooks Strain)—Intrapleural Inoculations. Six rabbits received intrapleural injections with cultures of the anaerobic streptococcus. The details are as follows. One cubic centimeter of a twenty hour culture of the Brooks strain of anaerobic streptococcus grown in a cooked meat medium beneath a petrolatum seal was injected into the right pleural cavity of one rabbit, and 3 cc into another. The first rabbit died within sixteen days, with massive empyema and abscesses of the mediastinum and of the mesentery. The anaerobic

streptococcus was recovered from the lesions in pure culture, it grew slowly and poorly aerobically but quickly anaerobically. The other animal was killed after six weeks and had a large walled-off empyema, the lung being destroyed on that side. Aerobic culture produced no growth, but there was good growth of the streptococcus under anaerobic conditions.

The cooked meat culture from the empyema in the first rabbit was then injected intrapleurally into another rabbit (3.5 cc), it resulted in the death of the animal in twelve days and the production of another massive empyema. The lung on that side was a consolidated, necrotic mass. There were also abscesses in the mediastinum and purulent pericarditis. The anaerobic streptococcus was recovered from each lesion in pure culture. Two and five-tenths cubic centimeters of the cooked meat culture from this empyema was then injected into the right pleural cavity of each of two rabbits. One died within five days of empyema, localized abscess between the heart and the diaphragm (this abscess contained gas) and acute fibrinous pericarditis. The other rabbit's chest was aspirated after one month, pus was obtained and the same streptococcus isolated. The animal was killed after two and a half months, when apparently in good condition. A large walled-off empyema was found, the lung on that side was necrotic, and there were some smaller abscesses in the mediastinum. Stained smear of this pus showed streptococci and gram-negative bacilli, but cultures gave no growth aerobically or anaerobically. The sixth rabbit of this series was given 3 cc of a culture of the streptococcus from the empyema of the fourth rabbit. The animal died within sixteen days, and autopsy showed empyema and abscesses of the mediastinum and of the wall of the chest. The right lung was necrotic.

A summary of the experimental empyemas produced in rabbits therefore shows that in each of 6 rabbits which received intrapleural injections of young (eighteen to twenty-four hour) cultures of the anaerobic streptococcus, massive empyema resulted. The empyema had the same characteristics in each case, except that in the cases of the rabbits surviving for a longer time it was surrounded by a more dense wall, and the pus had a much thicker consistency. Two of the 6 rabbits received injections of the original culture, while the other 4 received injections of cultures passed on from the empyema in the first animal. Each culture had the same characteristics. It was a granular growth in a cooked meat medium under a petrolatum seal, there was a small amount of gas and a moderately foul odor, and stained smears showed only streptococci in short chains. Two of the rabbits survived and were apparently in good condition when killed after six weeks and two and one half months, respectively, but the other four died within from five to sixteen days. The pus in each case was thick and white and did not have a foul odor. In only one case was gas found in any of the abscesses, and that was in an abscess between the heart and diaphragm. In 4 of the 6 cases there were also abscesses in the region of the mediastinum. In 1 there were abscesses in the mesentery. There were purulent pericarditis in 1 animal and fibrinous pericarditis in another.

In 1 rabbit the injection was made by mistake into the liver, and the animal was killed within three days when sick. A large multilocular abscess was found in the liver.

Subcutaneous Inoculations In 2 rabbits, approximately 0.5 cc of the culture was injected beneath the skin of the thoracic wall, and a hard, localized abscess was produced with no evidence of redness of the skin over it, the abscesses showed no tendency to progress and were found to contain thick, white pus.

Intracutaneous Inoculations Intracutaneous injection of 1 cc of culture in each of 2 rabbits produced abscesses which broke open within thirteen days and five days, respectively, and discharged thick pus. They healed within a few days.

Intravenous Inoculations Intravenous injection of 2 cc of cooked meat cultures of the streptococcus, containing small particles of meat, was made into the ear veins of 4 rabbits. The particles of meat were used purposely to serve as infected emboli. Two rabbits died within a few hours, no lesions were found at autopsy. In 1 rabbit, which died within three days, there was an infarct in the lung with fibrinous pleurisy, and in the fourth, which lived for nine days, there was a large abscess in each lower lobe and a walled-off empyema between each lower lobe and the diaphragm. Pathologic sections of the lungs showed abscesses with necrosis and colonies of bacteria which appeared to be only cocci. One mouse survived an intraperitoneal injection of 0.5 cc of culture of the streptococcus.

Comment—This case was one of extraordinary clinical interest. On admission the patient presented physical signs suggestive of fluid in the right pleural cavity. Thoracentesis subsequently revealed a putrid empyema. The mode of production of the empyema was not clearly understood. It was thought likely that an infection of the upper respiratory tract was followed by bronchopneumonia, with the formation of an abscess which ruptured into the pleural sac. One of the most unusual features of the case was, that, although myriads of bacteria (both gram-positive cocci and gram-negative bacilli) were found in smears of the original fluid, no growth was obtained in the usual aerobic cultures, but there was an abundant growth of a short-chained streptococcus in the anaerobic cultures. A comparison of the cultural characteristics of this streptococcus with others reported in the literature will be referred to later. This organism did not remain a strict anaerobe, for after repeated transplants it grew aerobically. This coccus was responsible for the production of multiple subcutaneous abscesses, pulmonary abscesses, osteomyelitis and endocarditis. The gram-negative bacillus, which was found only in the original stained smear of the empyemic fluid, failed to grow aerobically or anaerobically.

The presence of air in the multiple subcutaneous abscesses which developed during the patient's illness was a constant finding of special interest, since the streptococcus isolated from the lesions produced gas in anaerobic meat-broth cultures.

Empyema was produced in 6 rabbits by intrapleural inoculation of an anaerobic culture of this organism. The empyemic fluid was thick and white, as is characteristic of pus found in infections of rabbits. The empyema was of long duration in 2 rabbits, one of these animals was killed within six weeks when apparently in good condition, and the other within two and one-half months. The other 4 rabbits died within from five to sixteen days. By intravenous inoculation of rabbits with culture plus meat particles as emboli it was possible to produce pulmonary lesions in 2 of 4 rabbits.

Thus an anaerobic streptococcus has been shown to be the chief etiologic agent in this patient's illness, which was fatal. Although there were many other organisms in the pleural fluid, only one produced metastatic lesions, and this was recovered repeatedly from the blood stream.

CASE 2—History—C. B., aged 28, a white laborer, single, was admitted on Dec. 19, 1931, and died on December 31. The chief complaints were a catching pain over the chest and fever of four days' duration. The family history was noncontributory. The patient's general health had been excellent. He had always been obese, weighing 270 pounds (122.5 Kg.) for several years. He was examined a year before admission by his physician and found to be in good health. Two weeks before admission he contracted a cold with a severe cough. On December 15, four days before admission, he complained of a catching pain in the left side of the chest at the level of the eighth rib, the pain gradually grew worse. He went to bed because of shortness of breath and pain in the chest. The symptoms remained the same during the next two days. The day before admission the patient became much worse. The pain shifted to the upper left region of the chest and became more severe, the appetite failed, and there was fever and increasing dyspnea. The patient coughed little, and there was never any blood in the sputum.

Physical Examination—The temperature was 103.6 F., and the pulse rate, 130. The respiratory rate was 30, and the blood pressure, 154 systolic and 110 diastolic. The patient was a well developed, obese white man, sitting propped up in bed groaning with pain in the left side. He was oriented but seemed acutely ill. There was cyanosis of the lips and nail beds. There was no jaundice or petechiae. The tongue was coated, and the tonsils were large and edematous. A slight mucopurulent exudate was present in the pharynx. The chest showed restricted movement of the left side and signs of solidification of the left lower lobe. The heart was difficult to outline because of the obesity, but it did not appear to be enlarged. The sounds were of good quality, and no murmurs were heard. The pulse was rapid, equal and regular. There was no thickening of the radial vessels. Abdominal examination revealed nothing abnormal. The extremities were normal. There were also physical signs suggestive of Frohlich's syndrome, i. e., female crines, small genitalia, scant hair over the face and obesity.

The red blood cells numbered 5,200,000, and the white cells, 10,840. The hemoglobin was 100 per cent (Sahli). The differential count showed 85 per cent polymorphonuclears, 1 per cent polymorphonuclear basophil leukocytes, 6 per cent lymphocytes and 8 per cent myelocytes. The red cells were normal.

Urinalysis showed a dark amber color, specific gravity, 1.035, an acid reaction, sugar, 4 plus, albumin, 1 plus. Microscopic examination of the sediment showed a moderate number of white blood cells, there were no red cells, but there were occasional granular casts. Acetone and diacetic acid tests gave negative results.

A blood culture made under the usual aerobic conditions gave negative results. The Wassermann reaction of the blood was negative. A culture of the throat showed *Staphylococcus aureus*, *Streptococcus viridans*, *Micrococcus catarrhalis* and pneumococcus, group IV.

The diagnosis on admission was lobar pneumonia of the left lung, diabetes mellitus, hypertension and Frohlich's syndrome.

Course in the Hospital—An estimation of the blood sugar made immediately after the discovery of glycosuria showed 210 mg per hundred cubic centimeters of blood. Consequently vigorous efforts were made to control the diabetes through dietary regulation and insulin. Physical examination showed extension of the pneumonic process in the left lung. The patient's temperature remained high. The white blood cells numbered 17,300. On the third day after admission the temperature remained elevated, and the patient had more pain in his chest. A roentgenogram which showed a dense shadow occupying the entire left side of the chest suggested pneumonia and a large collection of fluid. The physical examination did not, however, suggest fluid. Cyanosis and dyspnea were more marked, and the patient was put in an oxygen tent. Sugar, acetone and diacetic acid were present in the urine despite large doses of insulin. On December 23 the patient was slightly improved. The physical signs were thought to be due to consolidation without fluid. During the next two days the fever continued to be high, the white cell count remained elevated, and all of the specimens of urine showed a 4 plus reaction of sugar. The patient's condition remained the same until December 30, when signs of fluid in the left thoracic cavity became definite, and thoracentesis was done. Thirty cubic centimeters of creamy, foul-smelling, purulent fluid was removed from the left side of the chest. Smears of the fluid showed gram-positive cocci in pairs and chains, gram-negative bacilli, fusiform bacilli, a few spirilla and many pus cells. A trocar thoracotomy was done immediately, and a rubber catheter was inserted in the chest and connected with the continuous tidal drainage apparatus (Hart). On the following day, December 31, the patient became much worse. His pulse was of poor quality. The respirations were rapid and shallow. There was marked cellulitis around the site of the thoracotomy incision, and this extended over a wide area of the anterior and posterior thoracic wall. The patient grew rapidly weaker and died that evening. A blood culture taken on the day of death remained sterile when incubated aerobically. Permission to perform an autopsy was refused.

Laboratory Studies—There was no growth from the pleural fluid aerobically on blood agar plate, or in beef infusion broth, in spite of the fact that many organisms were found on smear. Anaerobically in broth there was a granular growth at the bottom of the tube, and anaerobically on blood agar there were small colonies without the production of hemolysis. Smears of these colonies showed large gram-positive cocci, usually in pairs. The coccus was not bile-soluble. In cooked meat medium under petrolatum there was a rapid, diffuse growth with little or no gas and an extremely foul odor. Smears of the culture on meat medium showed mostly short-chained streptococci but also a moderate number of short gram-negative bacilli. This culture was transplanted to blood agar, and after two days in the anaerobe jar, two types of colony were found. One of these was found to be a pleomorphic gram-negative bacillus, possibly the influenza bacillus, and the other a gram-positive coccus. A pure culture of the coccus was obtained in meat medium, and this produced a granular growth with gas and little odor. The bacillus was not isolated in cooked meat mediums. It was thought that the anaerobic gram-negative bacillus, alone or in symbiosis with the streptococcus, was responsible for the foul odor of the cultures. The first culture of the streptococcus grew only anaerobically, but after being transplanted several times in cooked meat mediums it was found to grow aerobically also, though slowly.

Experiments in Animals—Intrapleural injections of 1 cc of cooked meat cultures of these organisms (predominantly anaerobic streptococci, but also a few anaerobic gram-negative bacilli) into a rabbit resulted in multiple pulmonary

abscesses on the side of the injection. There were pleural adhesions and an abscess of the anterior mediastinum. Anaerobic streptococci and gram-negative bacilli were recovered from the pulmonary abscesses and the mediastinal abscess. An injection of 4 cc into the right pleural cavity of another rabbit resulted in death of the animal within seventeen days with massive empyema. The fluid from the chest was semiwatery, grayish white and foul, and the empyema cavity was surrounded by a thick layer of fibrin. The lung on the side of the inoculation was a reddish, compressed, necrotic mass. A smear of the pus showed an abundance of streptococci and a moderate number of gram-negative bacilli. The streptococcus recovered from this empyema grew aerobically within three days and showed good growth anaerobically within twenty-four hours. It did not produce hemolysis. Intravenous injections of this organism into two rabbits, cultures on cooked meat mediums being used, with particles of meat for emboli, resulted in no pulmonary lesions. Intracutaneous injection failed to produce a lesion.

Comment—The patient was acutely ill on admission, and the signs of intoxication were marked. The pulmonary infection was complicated by a severe diabetes, which was difficult to control. A putrid empyema later developed for which thoracotomy was done with drainage of the large amount of fluid, but this failed to avert the fatal outcome, and the patient died with evidences of profound toxemia. A variety of organisms were found on smears of the empyemic fluid. Anaerobic culture yielded a streptococcus and gram-negative bacillus. The streptococcus was a facultative anaerobe. It was usually found with an anaerobic gram-negative bacillus (unidentified) but could be isolated in pure culture. It produced a small amount of gas with only a slight odor (when free of the bacillus) in cooked meat medium. It failed to produce hemolysis on blood agar. Cultures of the streptococcus produced a massive empyema in 1 of 4 rabbits on intrapleural inoculation and abscesses of the lung and mediastinum in another rabbit. Intravenous and intracutaneous inoculations gave negative results.

CASE 3—History—A P, aged 52, a colored cook, married, was admitted on Dec 5, 1932 and died on December 22. The chief complaints were pain in the left side and cough for three days. The family history was noncontributory. The patient's general health had been fairly good. He had an attack of jaundice at 7 years of age, malaria at 9 years, typhoid fever at 15 and right-sided pleurisy many years before admission. At 30 he had an illness described as rheumatism, which lasted for one and one-half weeks and involved the joints of the left leg, right arm and hand. He had been a heavy drinker for many years. For two weeks prior to admission he had felt unwell because of a cold and cough. On December 2, three days before admission, he had a shaking chill and a sharp pain in the lower part of the left axilla, accentuated by breathing. There were marked malaise and nausea, but no vomiting. The following day the thoracic pain persisted, the chills recurred, and the pain shifted to the upper part of the axilla. The patient vomited once on this day. On the day before admission, December 4, the cough became worse and was productive of a white phlegm. The sputum was never rusty or blood-streaked. On the day of admission, all of the symptoms became aggravated, and the patient was admitted to the medical ward.

Physical Examination—The temperature was 103 F. The pulse rate was 80 and the respiratory rate, 52. The blood pressure was 160 systolic and 110 diastolic. The patient was a husky colored man lying on the right side in acute respiratory distress. He was obviously ill but alert and oriented. Respirations were rapid, shallow and grunting, and there was dilatation of the alae nasi at every breath. He coughed up a small amount of foamy white sputum. There was no jaundice or cyanosis. The pupils reacted normally but were irregular. The mouth was foul because of dental caries. The pharynx was injected. The trachea was in the midline. The chest was well formed. There was great limitation of motion in the left region of the chest, particularly in the lower portion. The right side moved normally and was normal to percussion and auscultation. A leathery friction rub was heard in the left anterior axillary line. Anteriorly, the left region of the chest was normal, posteriorly, for three fingerbreadths above the normal base there was dullness to percussion, the breath sounds were high-pitched, and expiration was prolonged. The breath sounds were not definitely tubular. The heart was not enlarged. The point of maximum impulse was 8.5 cm to the left in the fifth space. The heart sounds were regular and slow. At the base the aortic and pulmonic second sounds were accentuated equally. The aortic second sound was ringing and preceded by a blowing systolic murmur. The abdomen was soft and not distended.

The red blood cells numbered 4,810,000, and the white cells, 12,760. The hemoglobin was 68 per cent (Sahli). The differential count showed juvenile polymorphonuclears, 6 per cent, adult polymorphonuclears, 65 per cent, monocytes, 7 per cent, and lymphocytes, 22 per cent. The red cells showed slight achromia. Urinalysis showed amber-colored and clear urine, specific gravity, 1.018, reaction, acid, sugar, negative, albumin, negative, in the sediment, no red blood cells, white blood cells in moderate number, with occasional clumping, and an occasional granular cast, acetone, negative, di-acetic acid, negative, bile, negative, urobilin, 4 plus.

The diagnosis on admission was lobar pneumonia of the left lower lobe on the fourth day of illness, chronic alcoholism, delirium tremens, arteriosclerosis and hypertension.

Course in the Hospital—For the first week of the patient's illness in the hospital, the temperature was constantly elevated, varying between 101 and 104 F, with corresponding tachycardia and a rapid respiratory rate. The white blood count during the first two or three days varied between 11,000 and 22,000. Three days after admission a pleuropericardial friction rub was heard over the left lower region of the chest. Cultures from the sputum showed green streptococci, *Staph aureus* and diphtheroids. No pneumococci were found. Roentgenograms of the chest showed consolidation of the left lung. On December 9 there was spread of the pneumonic process to the base of the right lung. On December 11 the patient was still acutely ill, with signs of solidification of the left lower lobe but fewer signs at the right base. He was semidelirious. On December 12 he lost about 200 cc of blood by rectum because of bleeding hemorrhoids. On December 13 he was disoriented and irrational. On December 15 the development of suppression of breath sounds and voice sounds and a flat percussion note at the right base indicated the presence of fluid. Thoracentesis was performed, but no fluid was obtained. On December 16 the temperature still varied between 100 and 102 F, and the physical signs in the lungs showed few changes. A friction rub heard at the apex of the heart was thought to be a pericardial rub. On December 17 it was noted that the patient's sputum, which previously had been mucopurulent and

occasionally blood-tinged, had become more purulent and extremely foul in odor. Physical signs showed a rapid respiratory rate, tympany at the left base posteriorly and an area at the angle of the left scapula where the breath sounds were faintly tubular. There were many râles of a metallic quality in this region. Pleural friction rub still persisted. Smears of the sputum showed numerous spirochetes and fusiform bacilli. In view of the atypical pneumonia it was thought that the patient probably had a pulmonary abscess. On December 18 he was given a transfusion of 500 cc of citrated blood without a reaction. On December 19, in view of persistent signs at the angle of the left scapula, a second thoracentesis was done, but no fluid was obtained. On December 20 the friction rub over the left side of the chest was still present, and the heart was found to be displaced to the right. Blood cultures taken on admission and on three subsequent occasions gave negative results. Roentgenograms of the chest showed "areas of consolidation involving the entire left lung with an area of lesser density suggesting lung abscess, bronchopneumonia right lung." On December 22 the patient complained of attacks during which he could not get his breath. He was exhausted and obviously weaker, the respiratory rate was as high as 80 per minute. The patient was coughing up a small amount of foul sputum. There was no deviation of the trachea. There were indefinite signs of solidification in the right middle lobe and signs of shifting dullness in the left side of the chest indicative of hydropneumothorax. A third thoracentesis was done in the left side of the chest, posteriorly. Three hundred cubic centimeters of creamy, brownish, fetid, purulent fluid was removed. During the process of removal a little air was obtained in the syringe, and when the patient coughed the plunger was forced outward with the air. More fluid could have been obtained, but the patient was so weak that the procedure was stopped. He died shortly after the thoracentesis.

Autopsy—The anatomic diagnosis was lobar pneumonia of both lungs and multiple abscesses of the left lower lobe, with organization of the surrounding exudate, a bronchial fistula and empyema on the left side and fibrinous pleurisy of the right side, an acute splenic tumor, hyperplasia of the bone marrow, multiple gummas and scarring of the liver, slight arteriosclerosis, and scars in the pancreas.

Laboratory Studies—The pleural fluid was grayish brown, moderately thick and foul in odor. A smear showed a predominance of gram-negative bacilli and gram-positive cocci. There were also a few fusiform bacilli. There was no growth aerobically, but when the exudate was inoculated into cooked meat medium under petrolatum there was a diffuse growth with gas and a foul odor. A smear of this showed gram-positive cocci (very small and often in short chains) and thin, rather long gram-negative bacilli. Anaerobic culture of this cooked meat culture on blood agar produced small colonies of viridans streptococci, the gram-negative bacilli did not grow on blood agar, aerobically or anaerobically. The anaerobic meat-medium culture was also transferred to blood agar and left under aerobic conditions. There was a slow growth in three days of fine colonies showing viridans hemolysis, which proved to be gram-positive cocci. The colonies of cocci from the anaerobic blood agar plate were then put into plain broth (not anaerobic) and in meat medium under petrolatum. In both there resulted a good growth without the production of gas or odor. The organism was not soluble in bile and produced acid in dextrose, maltose and sucrose but not in lactose or mannite.

A rabbit was given an intrapleural injection of 3 cc of the meat medium culture. The animal was killed two months later, but no lesion was found except a few pleural adhesions on the side of the injection.

Comment—On admission the patient was thought to have lobar pneumonia of the left lower lobe in the fourth day of the disease. The physical signs were not classically those of lobar solidification, however, and numerous cultures of the sputums with inoculations into mice failed to reveal pneumococci. As the disease progressed during the first week, pleural and pleuropericardial friction rubs were conspicuous. During the second week the sputum, which had formerly not been offensive, became foul. Physical signs over the left lower lobe plus the foul sputum suggested a pulmonary abscess, and this was confirmed by roentgenograms. During the third week the patient remained critically ill, and signs of a left hydropneumothorax developed. This proved to be a pyopneumothorax, as 300 cc of foul-smelling fluid plus air was removed from the left side of the chest. The suspicion at the time of death of confluent bronchopneumonia with pulmonary suppuration, a broncho-pleural fistula and putrid empyema was confirmed at autopsy. The autopsy showed numerous abscesses, one of which was in open communication with the pleura, and it was evident that the rupture of this abscess into the pleural cavity was responsible for the putrid empyema.

The empyemic fluid contained a number of organisms. Gram-negative bacilli and gram-positive cocci were in equal number, and there were similar numbers of fusiform bacilli. The smears of sputum showed numerous fusiform bacilli and spirilla. Cultures of the pleural fluid yielded a facultative anaerobic green streptococcus and an unidentified small gram-negative bacillus (possibly the influenza bacillus). The streptococcus was the only organism which could be carried on through subsequent cultures. Although at first it grew only anaerobically, subcultures later grew fairly well aerobically. This streptococcus alone or in symbiosis with other anaerobic organisms seems to have been responsible for the patient's pneumonia and empyema.

CASE 4—History—S. C., aged 53, a colored carpenter, was admitted on April 27, 1932. He was discharged on July 12. The chief complaints were shortness of breath and pain in the right side. The family history was not obtained. The patient was too ill to give an account of his previous condition. His general health, however, had been excellent. He was in good health until seven weeks before admission when he contracted a cold and had a sharp pain in the chest, accompanied by chill, malaise, fever and a cough with yellowish sputum. The illness was diagnosed as pneumonia by his physician. Within two weeks he was somewhat improved. Four weeks before admission a dull, aching pain developed in the right lower region of the chest and in the upper part of the abdomen. The cough persisted and was productive of mucoid but not purulent sputum. The appetite failed, pain persisted intermittently, he had frequent sweats at night and chills, and for a considerable period was delirious.

Physical Examination—The temperature was 102.4, the pulse rate, 102, the respiratory rate, 36, the blood pressure, 150 systolic and 98 diastolic. The patient looked acutely ill and complained of severe pain in the right side of the chest and the upper part of the abdomen. There were dyspnea, orthopnea and cyanosis.

An infrequent cough was productive of tenacious sputum. The teeth were in poor condition. The pharynx was injected. The heart was not enlarged, the rate was rapid but regular, and no murmurs were heard. The chest showed elevation of the left side of the diaphragm and normal pulmonary resonance on this side, on the right there was dulness below the fourth rib anteriorly and the seventh spine posteriorly, with distant to absent breath sounds and occasional coarse râles. The abdomen showed fulness in the right upper quadrant and an enlarged, tender liver. The spleen and kidneys were not felt. Large internal hemorrhoids and a firm prostate were found on rectal examination.

On admission the blood showed 3,520,000 red cells and 16,500 white cells. The hemoglobin was 55 per cent (8 Gm). The differential count showed polymorphonuclears, 61.7 per cent, myelocytes, 17.2 per cent, lymphocytes, 20.3 per cent and monocytes, 0.8 per cent. The blood smear showed that the red cells were smaller than normal, with central pallor. There was a shift to the left in the granulocytes. Urinalysis on admission showed yellow, clear urine, specific gravity, 1.013, reaction acid, sugar, negative, albumin 1 plus. Microscopic examination of the sediment showed a moderate number of white blood cells, but no red cells, and a moderate number of granular casts.

The diagnosis on admission was empyema at the right base, with possible subdiaphragmatic abscess on that side.

Course in the Hospital—A roentgenogram of the chest confirmed the impression of fluid at the right base. Thoracentesis was done immediately, and with the needle in the eighth interspace in the posterior axillary line 8 cc of thick, greenish-yellow, foul-smelling pus was removed. During that afternoon the patient had a shaking chill with a rise in temperature to 105 F. Trocar thoracotomy was performed, and a rubber catheter was inserted and connected with the continuous tidal irrigation apparatus (Hart). On April 28 there was considerable drainage of pus from the catheter. The patient was given a transfusion of 500 cc of citrated blood with no reaction. The number of white blood cells increased to 14,400. The temperature remained between 101 and 104 F. On April 29 the temperature was lower, but the patient was still critically ill. Physical signs in the chest had changed little. The respirations were rapid and shallow. The catheter was draining freely. The abdomen was markedly distended, and the tenderness in the right upper quadrant persisted. There was still thought to be a possibility of a subdiaphragmatic abscess, but no further operative procedures were done. During the next three or four days there was a gradual decline in the fever. The pulse remained accelerated. The white blood cell count remained between 16,000 and 20,000. The patient was delirious at times. Blood cultures taken on admission aerobically and anaerobically showed no growth. Culture of the sputum showed green streptococci and hemolytic and nonhemolytic staphylococci. The smears showed no acid-fast bacilli. On May 6 there were definite signs of improvement. The patient looked much better, but the temperature still remained elevated, and signs of solidification of the right lower lobe persisted. Abdominal distention was less, and the tenderness was somewhat reduced. On May 9 and 10 the temperature chart showed an evening peak of 103 F, with corresponding tachycardia. The cough was less, and the sputum not offensive or bloody. There were many moist râles at the left base posteriorly. The right side of the chest was clear anteriorly, but dulness and distant tubular breathing were still present posteriorly at the base. The rises in temperature suggested an area of pus which was not being adequately drained.

During the next week his condition changed only a little. On May 19, because of the patient's continued improvement and the diminution in drainage from

the chest, the use of the irrigation apparatus was discontinued, and the catheter left in place. Thoracentesis of the right side of the chest was again performed, but no fluid was obtained. Following the removal of the apparatus for drainage, the temperature fell to normal and remained there for three days. An abscess in the subcutaneous tissues surrounding the catheter was opened, and a large amount of pus evacuated, from which was grown *Bacillus pyocyaneus* and diphtheroids.

The patient continued to improve, and on May 31 the catheter in the chest was removed. The patient coughed up daily about 200 cc of frothy sputum. Smears were repeatedly negative for acid-fast bacilli. The signs in the lungs slowly cleared.

During the month of June convalescence continued. The temperature remained normal but tachycardia persisted. The electrocardiographic studies showed no abnormalities. On July 1 the patient was up and around the ward, feeling much improved. The cough and the pulmonary signs gradually cleared. The blood responded slowly to therapy with an iron preparation. The patient was discharged on July 12. Roentgenograms taken shortly before discharge showed only the evidence of a thickened pleura.

Laboratory Studies—The pus obtained from the pleural cavity was rather thick, greenish-white and foul. No spirochetes were found on smear or on dark field examination. Smears showed many gram-positive cocci in short chains. In addition, there were many groups of large curved, weakly gram-negative bacilli. They were always found in small groups, consisting of about ten organisms intertwined in a characteristic manner. These gram-negative bacilli did not grow in subcultures, and they were never identified satisfactorily, as they did not correspond to any organisms that we had observed in pleural fluids up to that time. Some observers thought they were fusiform bacilli, though they were weakly gram-negative. In some ways they resembled an organism described by Harris and Brown²⁹ and isolated from the uterus in 6 cases of puerperal infection. This was a pleomorphic gram-negative bacillus, often long and curved or beaded, and sometimes branching. They called it *Actinomyces pseudonecrophorus*, as it was much like *Actinomyces necrophorus*—an organism which is very pathogenic for animals and which produces lesions of a gangrenous and ulcerative character in many different species of animals. It is a strict anaerobe and is killed by a brief exposure to air. The possibility that this was the organism with which we were dealing became more plausible when we learned that Shaw has recently³⁰ reported the isolation of *A. necrophorus* from a pulmonary abscess in a man, and that it has been found responsible for various lesions in man, such as a pseudodiphtheria, abscesses of the tissues of the hip joint and retropharyngeal abscesses with gangrene.

Aerobic broth culture showed a slight growth of streptococci at the bottom of the tube, but there was no growth when this was transferred to blood agar. Anaerobically in cooked meat medium there was a diffuse growth of gram-positive cocci, with no gas and a moderately foul odor. Aerobic culture of the original pus on blood agar gave no growth, but subsequent culture on blood agar from the meat medium resulted in a slow growth of the streptococcus, with the production

²⁹ Harris, J. W., and Brown, J. H. Description of a New Organism That May Be a Factor in the Causation of Puerperal Infection, *Bull. Johns Hopkins Hosp.* **40**: 203 (April) 1927.

³⁰ Shaw, F. W. *Science* **77**: 392 (April 22) 1932.

of a small amount of hemolysis. Anaerobic culture on blood agar gave a good growth of pure culture of a green streptococcus.

The original pus injected into the pleural cavity of a rabbit produced large, walled-off empyema with thick white, odorless pus, a smear of which showed gram-positive cocci. Injection of this streptococcic culture (5 cc intrapleurally) into another rabbit gave negative results. Intravenous injection also gave negative results.

Comment—In this case the anaerobic streptococci were found in the pleural fluid in association with an unusual type of gram-negative bacillus which was never satisfactorily identified. No spilla were seen on smears of this fluid, and none was demonstrated in the sputums. The improvement of the patient was slow but definite under continuous irrigation of the pleural cavity with saline solution. He was discharged from the hospital after two and one-half months, greatly improved.

Brief mention may be made of three cases other than those of putrid empyema in which anaerobic streptococci were recovered. In 2 of them the organism was isolated from pus obtained from pulmonary abscesses at the time of operation, in the remaining case the organism was obtained from hepatic abscesses post mortem.

CASE A—The patient, H, had an acute pulmonary abscess. At operation foul, moderately thick pus was obtained. Smears of the pus showed many spirochetes, fusiform bacilli and gram-positive cocci. The cocci proved to be streptococci which grew slowly aerobically on blood agar. In beef infusion broth there was slight granular growth at the bottom of the tube. Anaerobically, in cooked meat medium and on blood agar, there was rapid growth with a slight amount of hemolysis. The cooked meat medium produced a diffuse growth with gas and a foul odor. The organism was found to ferment sucrose, dextrose, lactose and maltose, but not mannite. Two rabbits received intrapleural injections of culture of twenty-one to twenty-four hour cooked meat medium of this streptococcus. One was killed after one month, and the other after one and one-half months, though both animals appeared in good condition. In 1 an abscess was found in the pleuropericardial region, with adhesions to the right lung and heart. There was no growth from the pus, which was cultured aerobically, but anaerobically in meat medium there was a pure culture of streptococcus. Anaerobically on blood agar there was a growth of small colonies after four days. Smears of the colonies showed a short-chained streptococcus and a gram-negative bacillus which did not grow on subsequent subculture. In the other rabbit the only lesions found were pleural adhesions on the side of the injection. Intracutaneous inoculation of 0.5 cc of the culture of streptococcus resulted in a firm abscess with no redness of the skin.

This was therefore an organism which was found associated in the original pus with spirochetes and fusiform bacilli. In pure culture it was a streptococcus growing well anaerobically, with production of gas and a foul odor, aerobically it grew poorly. It was of low virulence for rabbits on intrapleural injection.

CASE B—The patient, S, had a chronic pulmonary abscess. Thick, brown, foul pus was obtained at operation. Smears showed spirochetes, fusiform bacilli and gram-positive cocci. Cultures resulted in the growth of a green streptococcus.

growing better anaerobically than aerobically (it grew aerobically only after repeated transplants), with no gas but with a foul odor on meat medium

CASE C—G, a white man, aged 25, was admitted because of fever, epigastric pain, chills, nausea and vomiting of seven days' duration. On admission he was acutely ill, with a temperature of 106 F and tachycardia of 124. Physical examination revealed little except tenderness in the epigastrium and leukocytosis of 50,000. The diagnosis on admission was obscure. The possibilities suggested were pneumonia, an infection in the kidney or an infection in or about the liver. The epigastric pain continued with nausea, vomiting, irregular fever and leukocytosis. The patient later became jaundiced. He died in uremia, with complete suppression of urine. Autopsy showed multiple hepatic abscesses, subacute appendicitis and thrombosis of the portal vein, with infection of the portal branches within the liver. Although three blood cultures were taken during life and incubated aerobically, none showed any growth. Cultures of the heart's blood and the hepatic abscesses at autopsy revealed two organisms: (1) an anaerobic beta hemolytic streptococcus fermenting lactose, dextrose, sucrose, salicin and maltose but not mannite, inulin or raffinose, this organism conformed to the *Streptococcus intermedius* of Prevot, and (2) an unidentified short, slender anaerobic gram-negative rod.

This case was puzzling clinically and was settled only by postmortem examination. The infection most likely began with an attack of appendicitis with subsequent pyelophlebitis and hepatic abscesses. The importance of incubating the blood culture anaerobically should be mentioned in this connection.

COMMENT

This report deals with the clinical and bacteriologic observations in 7 cases of putrid purulent infections from which anaerobic streptococci were isolated. Six of the patients suffered from acute respiratory infections, and 1 from hepatic abscesses. Anaerobic streptococci were the only organisms recovered culturally in 6 of the cases, and in the other they were abundantly present with a mixed flora. The significance in pathogenesis, which the predominance of this type of bacteria suggested, was supported by experimental results in rabbits.

The 4 patients who had putrid empyema were men, 3 of them died. In the cases with a fatal outcome the duration of the disease was from sixteen days to two months. The patient, who recovered, had a prolonged illness which lasted four months.

From the clinical standpoint the cases are of interest in that the putrid empyema developed acutely and suddenly and was not a complication of a preceding chronic pulmonary infection. The studies indicated, however, that the pleural infection was associated with intrapulmonary infection. This relationship was proved in 2 of the cases which were examined post mortem.

The fluid aspirated from the pleural cavity had a characteristically offensive odor and was moderately thick, varying in color from brownish-gray to green. A stained smear of this pus at the time of the first aspiration in each case revealed myriads of bacteria of various

types Spirochetes and fusiform bacilli were found in 2 cases, and a gram-negative bacillus (usually short but at times long and thin) was present in 3. There was a gram-positive coccus (usually predominating) in all 4 cases. In 1 there were in addition to the coccus, many small groups of long, curved gram-negative bacilli, these were always found in isolated groups and were intertwined in a characteristic manner.

Bacteriologically, the cases were complex. It seems to us of interest, however, and probably significant, that anaerobic streptococci were present in each case, although the associated organism, which constituted the flora, was not consistently of one type. Furthermore, that the method of laboratory cultivation is of special importance is demonstrated by the fact that streptococci were chiefly recovered under anaerobic conditions, when the usual aerobic methods failed. The results are illustrative of the importance of considering cultural and environmental factors when one attempts to isolate bacteria from pathologic lesions. Of the four strains of streptococci, two were viridans, one nonhemolytic and one hemolytic. They grew in short chains and produced a granular growth in cooked meat mediums beneath a petriolatum seal, usually with a foul odor. Though they could be grown only slowly or not at all under aerobic conditions, subsequent transplants from the original fluid showed a definite though slow growth aerobically. There was always a luxuriant growth anaerobically. In biologic and cultural characteristics they resemble in some ways the *Streptococcus putridus* of Schottmüller and the *Streptococcus intermedius* of Prévot. The latter organism was found in pulmonary conditions, but both these types are described as strict anaerobes, whereas ours were facultative anaerobes. Another of Prévot's group is referred to as "anaerobes by predilection," the first cultures growing only anaerobically, while subcultures grow aerobically also. This group Prévot called "*Streptococcus evolutus*," and most of the strains were isolated from pulmonary conditions. If an attempt is made to classify the streptococci which we are reporting under any one heading, they would seem to correspond to the latter group more closely than to any other.

We have reviewed the subject of putrid empyema because it is not an extremely uncommon sequel to pulmonary suppuration of various types, when it develops, the prognosis becomes grave. We have also made special reference to an anaerobic streptococcus which was found in the 4 cases reported because it is an organism that is found throughout the body in various putrid and gangrenous lesions. Its presence is apt to be overlooked unless anaerobic cultures are taken. Our studies indicate that it was the chief etiologic agent in the 4 cases of putrid empyema, in 1 of which it invaded the blood stream, produced multiple metastatic abscesses and endocarditis and was obviously the cause of death.

Although the therapeutic side has not been emphasized in this report, surgical drainage would seem to offer the best chance of cure. Intravenous injections of neoarsphenamine are probably of value in cases in which spirochetes are found, especially if they are also in the sputum. Extensive cellulitis of the thoracic wall, with the formation of gas, may follow surgical drainage or aspiration, owing to the leakage of the organisms along the path of the needle or the incision. A therapeutic procedure that may offer additional help in dealing with such effusions, swarming as they are with anaerobes, is the replacement of the empyema by air. We have had no experience with this form of treatment of empyema, but favorable results have been reported by Danna and others in all forms of empyema.

SUMMARY

1 Attention is called to the fact that infections due to anaerobic streptococci may occur frequently and fail to be recognized unless cultivation is properly performed.

2 A case is reported of putrid empyema with pulmonary abscesses, septicemia and metastatic putrid abscesses due to a gas-producing, facultative anaerobic streptococcus.

3 Other cases of putrid empyema are reported in which an anaerobic streptococcus was found in conjunction with other organisms.

4 Anaerobic streptococci were found to be the predominant organisms in 2 cases of pulmonary abscess in which cultures were made directly from the pus at operation. Other authors have stressed the frequent occurrence of these organisms in such lesions.

5 Although the finding of anaerobic streptococci in cases of pleural and pulmonary disease has been emphasized, the literature indicates their frequent occurrence in other infections, notably in cases of puerperal sepsis or septic abortion, otitis media, pulmonary abscesses and hepatic abscesses.

6 Mention is also made of a case of pylephlebitis with multiple hepatic abscesses due to an anaerobic streptococcus. An attempt is made to identify the streptococci reported with various types described in the literature. They do not completely fulfil the characteristics of any one group.

7 Cultures of one strain were capable of producing empyema in rabbits when injected intrapleurally. Other strains gave varying results under similar conditions.

8 Evidence is presented to indicate that these streptococci may often be pathogenic for man and for animals.

UNILATERAL AND BILATERAL RESECTION OF THE MAJOR AND MINOR SPLANCHNIC NERVES

ITS EFFECTS IN CASES OF ESSENTIAL HYPERTENSION

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On the basis of postmortem investigation and theoretical consideration, section of the splanchnic nerves was suggested by Jean¹ in 1921 for the relief of pyloric spasm, hyperacidity and hypersecretion. In 1923 Daniélopou,² considering the importance of the splanchnic nerves in the regulation of arterial pressure, conceived the idea of their resection in the treatment of hypertension. In the same year, Bruning³ suggested the same surgical procedure, and in 1924 Pende⁴ proposed before the Congress of Internal Medicine at Milan surgical treatment of arterial hypertension which consisted of resecting the left splanchnic nerves. In 1927 Pieri⁵ performed unilateral resection of the splanchnic nerves for intestinal atony. In 1930 Pieri,⁴ following the suggestion of Pende, successfully resected the left splanchnic nerves of two patients suffering from arterial hypertension. In 1932, Durante,⁴ of Genoa, resected the large and small left splanchnic nerves of two patients suffering from different arterial diseases. These cases were reported by Santucci,⁶ and although they were not true cases of hypertension, the postoperative observation indicated a fall in both systolic and diastolic pressures. In giving a résumé of the surgical techniques which have been described in the literature, Pereira⁷ stated that

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1 Jean, G. Les nerfs splanchniques au point de vue chirurgical, *Arch de méd et pharm nav* **111**:292, 1921

2 Daniélopou, quoted by Pereira⁷

3 Bruning, Friedrich, and Stahl, O. Die Chirurgie des vegetativen Nervensystems, Berlin, Julius Springer, 1924

4 Quoted by Santucci⁶

5 Pieri, Gino. La resezione dei nervi splanchnici, *Ann ital di chir* **6** 678 (July) 1927

6 Santucci, Gastone. La thérapeutique chirurgicale de l'hypertension artérielle selon la méthode de Pende, *Clinique, Paris* **27** 9 (Jan) 1932

7 Pereira, António. Nervi splanchnici, Porto, Portugal, Tipografia Porto Medico, Ltd, 1929

Pieri's technic consisted of resection of the splanchnic nerves by means of the supradiaphragmatic approach after resecting the tenth, eleventh and twelfth ribs. Rossi⁸ attacked the splanchnic nerves between the attachments of the diaphragm after resecting the transverse process of the eleventh and twelfth thoracic vertebrae and the twelfth rib when necessary. Pereira objected to the two previous technics because of the danger of injuring the pleural sac and proposed section of the splanchnic nerves below the diaphragm without resection of bony structures.

In 1925 Rowntree and Adson⁹ performed bilateral lumbar sympathetic ganglionectomy on a patient with hypertension. The beneficial effects were only transient, and later Adson attempted to relieve hypertension associated with severe headaches by removing the cervicothoracic sympathetic ganglions. In both cases it was the opinion that insufficient vascular areas had been affected by the operation. In 1930 Adson and one of us (Craig) divided the right and left anterior roots of spinal nerves from the sixth thoracic to the second lumbar ganglions, the patient was a young adult who had a severe form of essential hypertension. The operation was followed by definite improvement in the hypertension, but, because of the manipulation of the spinal cord that it entailed, extensive resection of the nerves was not considered a satisfactory method of combating the changes in the blood pressure.

The splanchnic nerves are composed of preganglionic fibers which emerge from the spinal cord through the anterior roots and enter the thoracic sympathetic ganglionated trunk by means of communicating rami. These fibers traverse the ganglions and make their exit by means of fibers given off by the fifth to the twelfth thoracic ganglions. The major splanchnic nerve is usually composed of fibers from the fifth to the tenth ganglions, and the minor splanchnic nerve of fibers from the last two dorsal ganglions. The splanchnic nerves leave the thoracic cavity and enter the abdominal cavity between the crura of the diaphragm. It is at this point that resection is carried out.

PATHOGENESIS OF ESSENTIAL HYPERTENSION

Of the various hypotheses concerning the etiology of essential hypertension, the most acceptable is that the condition is of neurogenic origin. Hypersensitivity or hyperreactability of the vasomotor nervous mechanism is postulated. Whether this abnormality is of central origin, that

8 Rossi, Ferdinando. La resezione del tronco simpatico toracico e dei nervi splanchnici nello spatium inframediastinale posterius, *Arch ital di chir* **21** 729, 1928, abstr, *Zentralbl f Chir* **56** 1334 1929.

9 Rowntree, L. G., and Adson, A. W. Bilateral Lumbar Sympathetic Neurectomy in the Treatment of Malignant Hypertension, *J A M A* **85** 959 (Sept 26) 1925.

is, whether there is a hypersensitive vasomotor center, lowered tonus of the cardio-aortic and carotid sinus reflex zones or some abnormality of the peripheral mechanism, is not known. The experimental evidence of Raab¹⁰ is that an increase in the concentration of carbon dioxide in the blood augments the vasopressor effects by action on the vasomotor centers. Similar increase in the reactions of hypertensive subjects is obtained by means of stimulation by cold.¹¹ Clinical evidence favors a central basis for the abnormality in essential hypertension for the following reasons: 1. The vasoconstrictor disturbance is widely distributed. 2. Analogies to other sympathetic disturbances of the central mechanism exist, such as disturbance of the heat-regulating centers in certain lesions of the brain. 3. Demonstrable pathologic abnormalities in the arterioles, endocrine glands or sympathetic nerves of subjects with the earliest forms of hypertension are not found. It is probable that after organic changes have occurred in the arterioles, peripheral pressor effects constitute a superimposed pressor factor. Renal sclerosis and insufficiency add a further peripheral pressor element. The part played by pressor hormones is not clear, but may be important. Although the etiology of the fundamental pathologic change is unknown, attempted control of the abnormal central vasopressor reactions is logical. A similar problem exists in Raynaud's disease, control of which is made possible by blocking the efferent pathways to the vessels. In the early stages of this disease, evidence indicates hyperreactability of the centers in the spinal cord. At this stage, resection of the sympathetic ganglions effects clinical cure. In the more advanced stages, Lewis¹² wrote, a peripheral "fault or demonstrable organic occlusion of the smaller digital arteries superimposes an additional factor, not completely controlled by section of the sympathetic nerves."

RATIONALE OF SPLANCHNIC SYMPATHECTOMY

Maintenance of the blood pressure involves two mechanisms. One mechanism maintains the systemic blood pressure at optimal levels. The factors involved in this are multiple. Maintenance of blood pressure is not materially affected by removal of the sympathetic nerves, as has been shown by Cannon.¹³ The other is a mechanism of response, involv-

10 Raab, W. Central Vasomotor Irritability, Contribution to the Problem of Essential Hypertension, *Arch Int Med* **47** 727 (May) 1931.

11 Hines, E. A., Jr., and Brown, G. E. A Standard Stimulus for Measuring Vasomotor Reactions. Its Application in the Study of Hypertension, *Proc Staff Meet*, Mayo Clin **7** 332 (June 8) 1932.

12 Lewis, Thomas. Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers, a Variety of Raynaud's Disease, *Heart* **15** 7 (Aug) 1929.

13 Cannon, W. B. Personal communication to the authors.

ing rapid increases of the blood pressure to stimulation psychic, sensory and otherwise. It is the "response" or vasopressor reactions which we wish to emphasize in writing of the therapeutic endeavors in hypertension.

Recent studies have shown that the hypertensive response of the blood pressure in cases in which the earliest forms of essential hypertension are present is the sole abnormality as yet demonstrated. With a standard stimulus (local application of cold) it has been shown that the blood pressure of normal subjects and of patients with diverse types of diseases momentarily increases, the increase averages 10 mm of mercury systolic and 8 mm diastolic. In the cases of mild or early essential hypertension the average increase is three times greater than this. In the more advanced types of hypertension, increases of from three to six times the normal response are obtained. A group of young subjects from 16 to 30 years of age, apparently normal, in the immediate families of 75 per cent of whom hypertension had appeared, have had reactions of the same magnitude as have subjects with early hypertension. These we have called the "hyperreactive normals." This suggests that the vasopressor mechanism of subjects predisposed to essential hypertension is constitutionally abnormal, the abnormality expressing itself as an excessive reaction to stimulation. The reaction is of the same order as that of normal subjects, except that it is magnified. If this is true, this functional stage of essential hypertension assumes an important part in the explanation of the evolution of the disease and of the subsequent organic changes in the arterioles. These excessive reactions constitute abnormal degrees of arteriolar "wear and tear." The problem of treatment of hypertension, then, will involve endeavors to block or modify these excessive responses before the onset of organic or irreversible lesions in the arterial tissues, with ensuing high blood pressure.

Selection of Cases (Theoretical Consideration)—In the clinical forms of essential hypertension, two groupings are possible, the functional or "preorganic" and the organic types. This distinction can be made on the basis of the appearance of retinal arterioles and by quantitative studies of the arterioles in a specimen of muscle removed for biopsy. In some cases this division is clear, in others, both organic and spastic elements are present. The existence of a spastic form of retinitis, as described by Wagener in organic types of hypertension, has helped to clarify this concept. The excessive response of blood pressure to stimulation has given further evidence of the spastic element in certain types of essential hypertension. Certain subjects with hypertension have periods in which the blood pressure is excessively labile. The problem in selection of the type of subject who is suitable for resection of the splanchnic nerves entails recognition of the degree in which the case exemplifies these two factors, the spastic or vasomotor

and the organic. The first is concerned with abnormal fluctuation of the blood pressure and the second with levels of the blood pressure attained under resting or basal conditions. To evaluate these components before operation is important, for removal of the vasomotor control of the splanchnic bed would, theoretically, modify only the vasomotor element.

Procedures—The maximal reactions of the blood pressure are determined by application of cold and by carbon dioxide tests. The increase and the maximal level attained then become the criteria with which the effects of subsequent therapeutic measures can be compared. Hourly readings of blood pressure are taken for twenty-four hours under controlled conditions, and the mean resting levels and hourly fluctuations are determined.

In spinal anesthesia procaine hydrochloride in doses of from 60 to 75 mg is employed. The blood pressures are taken every fifteen minutes, and the cold test is repeated at frequent intervals. With anesthesia to the level of the nipple the responses of the blood pressure to cold are greatly reduced or obliterated, and the splanchnic chemical denervation should be complete. In addition to anesthetization of the sympathetic nerves the motor and sensory fibers of the lower limbs and abdominal wall are also temporarily blocked. Vasodilatation of the surface vessels of the toes is taken as evidence that the sympathetic nerves are anesthetized. Emmett's¹⁴ studies with spinal anesthesia revealed that sympathetic, sensory and motor nerves are anesthetized in the order named. Preoperative studies with spinal anesthesia were made to obtain information concerning the extent cephalad to which anesthesia must be induced to diminish or inhibit the pressor reactions and to determine the probable effects of splanchnic denervation on these responses. The organic changes are evaluated by measurements of the arterioles in a specimen of muscle removed for biopsy, by the appearance of the arterioles in the ocular fundi and by the basal blood pressures. The age of the patient and the function of the heart or kidneys and other clinical criteria are of major importance in deciding on operability.

RESECTION OF SPLANCHNIC NERVES AND POSTOPERATIVE COURSE

The technic which we have adopted consists of the posterior, infradiaphragmatic approach, with the incision in the skin extending from the level of the eleventh rib to the crest of the ilium, about 6 cm from, and paralleling, the spines of the vertebrae. The posterior layer of the lumbodorsal fascia is incised almost to the level of the twelfth rib above and to the crest of the ilium below, and the fibers of the serratus posterior inferior muscle are divided, exposing the sheath of the sacrospinalis muscle. This sheath is then divided about 2 cm mesial to the lateral

¹⁴ Emmett, J. L. Subarachnoid Injections of Procaine. The Quantitative Effects of Clinical Doses on Sensory, Sympathetic and Motor Nerves, J. A. M. A. 102:425 (Feb. 10) 1934.

border of the muscle. The muscle is then retracted mesially, exposing the anterior layer of the lumbodorsal fascia, which, when incised, exposes the quadratus lumborum muscle. This muscle is split longitudinally, and the peritoneum is exposed. With a cotton pledget the peritoneum is gently dissected away from the quadratus lumborum muscle until the edge of the psoas major muscle is exposed. The dissection is carried still farther toward the median line, until the vertebral column is encountered, which is usually about the level of the second lumbar vertebra. The crura of the diaphragm are attached to the first and second lumbar vertebrae, so the dissection is turned upward at this point until the crura are exposed. Descending from above downward, between the crura, are the splanchnic nerves. Sometimes they occur singly or fused into one large trunk, and by elevating the perirenal fascia and placing the nerves on tension, 3 or 4 cm can be resected.

Following this, the dissection can be carried downward and the lumbar sympathetic chain exposed by retracting the psoas muscle laterally. The first and second lumbar sympathetic ganglions can then be resected.

In the majority of cases the postoperative course is uneventful, and the patients are up and about in from six to ten days. The only case in which there was any difficulty following operation was one in which the nerves were small, and in order to be sure that sufficient amounts of them had been resected, the exposure was carried up into the pleura, and a transient pneumothorax complicated the convalescence.

REPORT OF CASES

CASE 1—A man, aged 39, came to the clinic in September 1930 because of high blood pressure that had first been discovered eight years previously. The patient's father had died of hypertension, and one sister had hypertension. Eighteen months before admission the patient had noticed "fulness in the head," dizziness, insomnia, apprehension and daily headaches.

When taken hourly for twenty-four hours, the blood pressure was 185 systolic (mean) and ranged from 150 to 220, the diastolic pressure was 125 (mean) with a range of from 110 to 145. The enlargement of the heart was graded 1, and the sclerosis of the retinal arteries, of the hypertensive type, was of grade 2. Renal insufficiency was not demonstrable. The patient was treated medically by means of rest and sedatives, and his diet was restricted.

The patient returned to the clinic about two years later. During the interval he had taken his own blood pressure from time to time, it revealed a progressive, widely fluctuating, severe type of hypertension. The headaches had persisted, and moderate dyspnea was present on exertion. Hemoptysis had occurred four months previously, and vision had become blurred, the latter condition had lasted from one to six hours. The retinal arteries were examined by Dr Wagener, who found sclerosis graded 2, generalized retinal spasm, slight edema of the disks and a few hemorrhages and exudates. The systolic blood pressure was 210 (mean) and ranged from 170 to 245, the diastolic pressure was 145 (mean) and ranged from 120 to 180 (fig 1). The electrocardiogram revealed inversion of the T wave in lead I. There was no renal insufficiency, and there were no formed elements in the urine.

The patient returned a month later for operation. The response of the blood pressure to local application of cold consisted of an increase from 210 to 245 systolic and from 150 to 170 diastolic (fig 1).

On Oct 26, 1932, the left major and minor splanchnic nerves and the twelfth thoracic or first lumbar ganglion were resected. The postoperative course was uneventful. Fourteen days after operation, hourly readings revealed that the

systolic blood pressure was 185 (mean), with a range of from 170 to 205, the diastolic blood pressure was 135 (mean), with a range of from 120 to 150. The headaches had entirely disappeared. After fourteen days the patient was walking about, his general condition was satisfactory. There was no change in the appearance of the vessels of the ocular fundi, and the patient was allowed to return home on November 10.

Three months later the patient returned for resection of the right splanchnic nerves. Since his first operation he had been fairly active, but the headaches had recurred in the morning. He had had a severe attack of influenza during this interval, on the second day of which blurring of vision of the left eye had developed and persisted. The retinal arteries were markedly narrowed, with sclerosis graded 2 and 3, recurrence of angiospastic retinitis, fresh cotton-wool hemorrhages and exudates and edema of the disks. Urinalysis revealed the presence of albumin, graded 2, with an occasional hyaline cast. The concentration of urea was 28 and

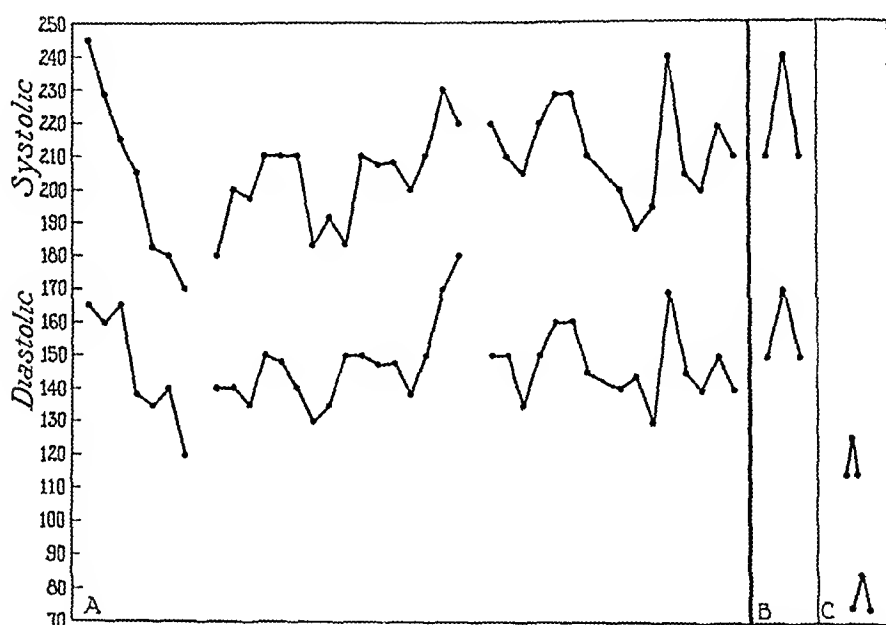


Fig 1 (case 1) —A, hourly systolic and diastolic blood pressures before operation, B, response to the application of cold, C, results of a cold test in a normal person

50 mg in each 100 cc of blood. In the electrocardiogram the T waves were inverted in leads I, II and III. The blood pressure was 210 systolic (mean) and ranged from 195 to 230, the diastolic pressure was 160 (mean), with a range of from 140 to 180 (fig 2 A). With the cold test the blood pressure increased to 240 systolic.

On Jan 23, 1933, the right major and minor splanchnic nerves were removed. The right sympathetic cord, at the level of the first lumbar ganglion, also was resected. Observations during operation revealed sharp responses in systolic pressure following manipulation of the splanchnic nerves (fig 2 B). Following resection of the minor splanchnic nerve there was a sharp drop of 40 mm in the systolic blood pressure, and following resection of the greater splanchnic nerves there was a further drop of 30 mm to 130 systolic and 105 diastolic. The patient's general condition was satisfactory after the operation. There was no evidence of shock. The blood pressures were taken hourly during the entire postoperative period. At the end of the fifth day the blood pressure had returned to a systolic

mean of 205 and a diastolic mean of 135. At the end of fourteen days the patient was up and about. Determinations of blood pressure when the patient had exercised showed 190 systolic and 135 diastolic. The responses of the blood pressure to stimulation by cold gradually increased from the first to the fourth day and then remained constant (fig 3). At the time of dismissal there was no significant change in the retinal vessels except thrombosis of a small retinal vein.

Clinically, the patient seemed somewhat improved. The headaches in the morning had disappeared. The value for blood urea was slightly high, and the urine revealed albumin and casts. The function of the gastro-intestinal tract was not disturbed. After his return home the patient was carefully observed by Dr Crawford of Tulsa, Okla. There was no further drop in blood pressure. There was slight recurrence of the headaches in the morning, and in a letter dated April 27 it was stated that the patient had lost the sight of the left eye. A rather severe degree of hypertension had developed. The patient died in July 1933, probably of renal insufficiency.

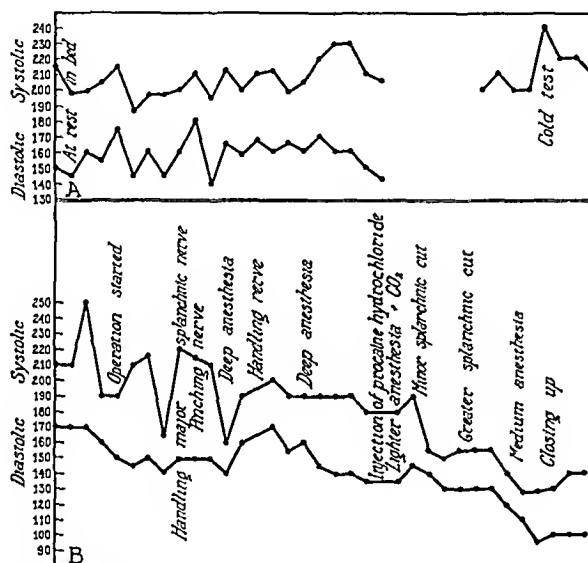


Fig 2—A, hourly blood pressure and response to the application of cold three months after resection of the left major and minor splanchnic nerves and the twelfth thoracic ganglion, B, sharp response in systolic pressure during the operation, with manipulation of the splanchnic nerves. The fundi showed constriction of the retinal arteries, grade 3, sclerosis, grades 2 and 3, recurrence of angiospastic retinitis, edema, exudates and hemorrhages. There was an inverted T wave in leads I, II and III.

The measurements of the arterioles in a section of muscle removed at operation revealed a ratio of lumen to wall of 1.12 as compared with the normal of 1.05 (fig 4). According to Keith's grouping of the organic forms of hypertension, based on examination of the retina and measurements of arterioles, this case would fall in group 3, a borderline group of malignant forms of hypertension.

Comment—The studies in case 1 are of interest from the physiologic standpoint. The presence of a severe form of hypertension, with marked hypertrophy of the media of the arterioles and other findings, indicated a malignant form of hypertension. The effect of resection of the left

splanchnic nerves revealed moderate reduction in the responses and in the levels of the patient's blood pressure. Several months later an infection which exerted a deleterious effect on the severity of hypertension developed, and mild renal insufficiency, spastic retinitis and significant changes in the electrocardiogram were noted. The second operation was carried out during this phase. Within two weeks there was gradual restoration of the levels of blood pressure and responses to the values before operation. The clinical responses in this case were not encouraging, it seems reasonable to suppose that during this stage the neurogenic factor in the hypertension was of minor importance. The hypertrophic changes in the media of the arterioles and the development of infectious toxemia with the onset of renal injury suggest that peripheral factors became predominant and were the major factors in initiating and main-

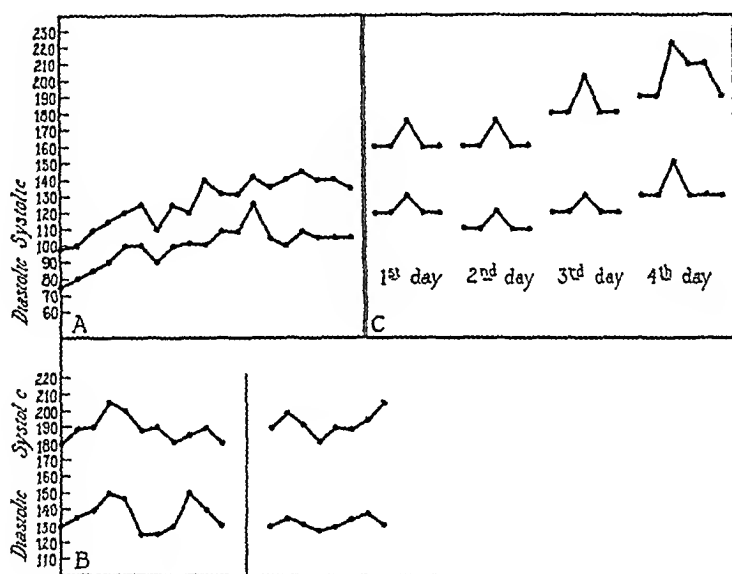


Fig 3—Hourly readings of the blood pressure after resection of the right splanchnic nerves. A, first day after, B, two weeks after, C, cold tests following operation

taining high levels of blood pressure. It seems likely that the renal insufficiency had nullified the depressor effects of the bilateral operation. It is of interest that unilateral resection of the splanchnic nerves did not prevent or apparently change the course of progressive renal disease.

CASE 2—A woman, aged 34, of Syrian ancestry, knew of no family history of hypertension. At the age of 23, when pregnant for the second time, mild toxemia developed, and the systolic blood pressure rose to 200. Following delivery, the blood pressure was 130 systolic, and the patient felt well. A third pregnancy five years later was uneventful. Three years after the third pregnancy the systolic blood pressure was 185 and the patient had headaches in the morning. After that the systolic blood pressure varied between 150 and 200. Seven weeks before admission to the clinic visual disturbances of the right eye developed, with severe occipital headaches and vertigo.

Examination revealed narrowing and sclerosis, graded 1, of the retinal arteries of the hypertensive type. Residual edema and a macular star, the residue of angiospastic retinitis of the right eye, were present¹⁵. The heart was enlarged to grade 1. Roentgenograms of the thorax revealed diffuse dilatation of the aorta.

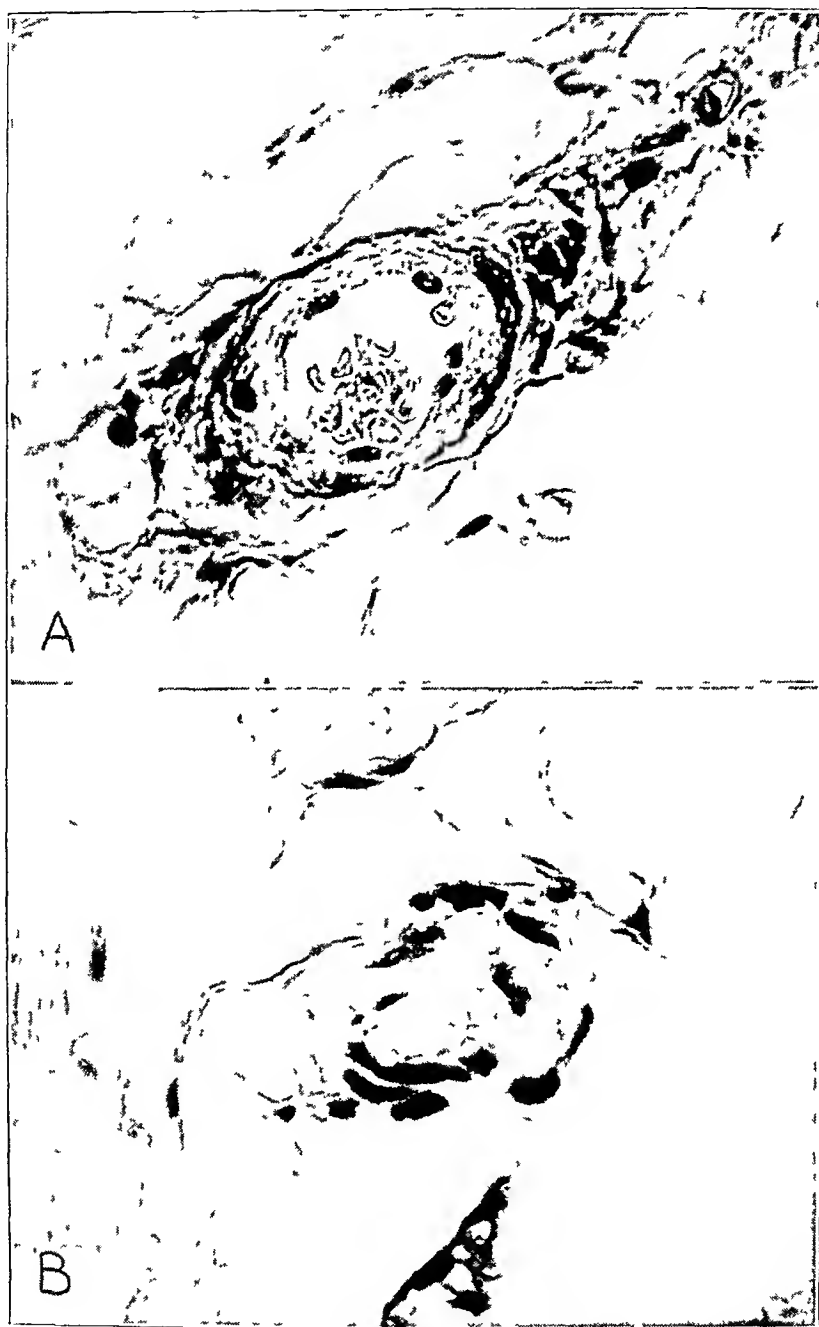


Fig 4—Photomicrograph showing the ratio of the arteriolar lumen to the wall
A, normal ratio, B, ratio in case 1

15 Wagener, H P, Barker, N W, and Burke, C F. Acute Angiospastic Retinitis. Occurrence in Cases of Severe Hypertensive and Renal Disease, *Am J M Sc* **185** 517 (April) 1933

Albumin in the urine was graded 2, there was no impairment of the ability of the kidneys to excrete urine. No significant changes were observed in the electrocardiogram.

Hourly determinations of the blood pressure under controlled conditions for forty-eight hours revealed a mean systolic pressure of 200, with a range of from 160 to 225 and a mean diastolic pressure of 135, with a range of from 120 to 150 (fig 5). The response to cold was 50 systolic and 30 diastolic, with maximal readings of 230 systolic and 150 diastolic. Spinal anesthesia with 60 mg of procaine hydrochloride reduced the blood pressure to 140 systolic and 100 diastolic, with a reduction of the response to cold to normal values of 10 systolic and 8 diastolic.

The left major and minor splanchnic nerves were resected on Dec 1, 1932, in addition, the first lumbar sympathetic ganglion was removed. Manipulation of the splanchnic nerves during operation increased the systolic pressure 50 mm and the diastolic pressure 30 mm. Sectioning the nerves was followed by a fall of 50 systolic and 30 diastolic (fig 6).

On the day following the operation the response to cold was 40 systolic and 20 diastolic, with a maximal level of 190 systolic and 130 diastolic. The patient

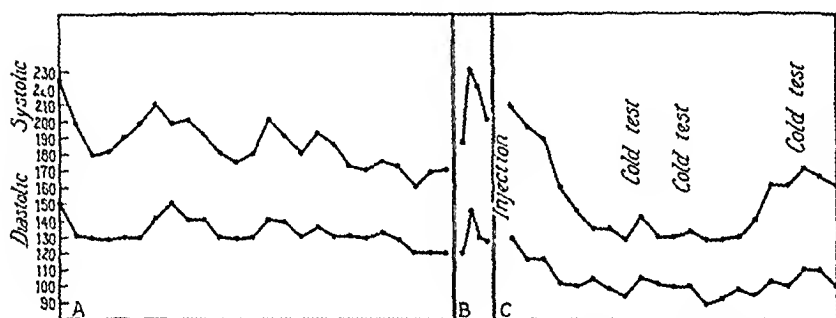


Fig 5 (case 2) — *A*, hourly determinations of blood pressure during rest, *B*, cold test, *C* effect of spinal anesthesia (analgesia to the second dorsal segment). The fundi showed mild angiospastic retinitis, constriction of the retinal arteries with sclerosis, grade 2, and residual edema.

recovered uneventfully and was dismissed on the fourteenth day after operation. Examination of the ocular fundi at the time of dismissal revealed that most of the retinal arteries were of good caliber, sclerosis was graded 2 in the smaller branches, and there was a residual cotton-wool patch in the right disk. The headaches and dizziness had entirely disappeared. Vision had improved. There was no significant change in the blood pressure with changes in posture. The responses to cold were 180 systolic and 120 diastolic.

The patient returned for reexamination three months later. The symptoms were completely relieved. There had been no untoward disturbances in the gastrointestinal or genito-urinary tracts. Menstrual flow had increased in amount. Examination of the ocular fundi revealed that the retinal arteries were of good caliber. Some constriction in smaller branches and few residual exudates were seen. Under stimulation with cold the blood pressure was 40 systolic and 12 diastolic, with a maximum of 206 systolic and 126 diastolic. One year after operation the clinical improvement had remained unchanged.

The clinical condition of the patient was so satisfactory that operation on the right side was deferred.

Comment—The patient in case 2 had a severe form of essential hypertension, with mild organic changes in the arterioles. Following resection of the left splanchnic nerves, unquestionably the reaction of the blood pressure to cold was lowered, as were the mean levels of blood pressure, which had persisted for three months. Relaxation of the retinal arteries was definite. It is interesting that the operative effects seemed more conclusive following operation on the left splanchnic nerves than on the right, as in case 3. The increase in menstrual flow following operation is of interest.

CASE 3—A woman, aged 33, a nullipara, had known for eight years that she had hypertension. During this period she had been observed from time to time at the clinic, the levels of blood pressure were slowly progressive, the diastolic

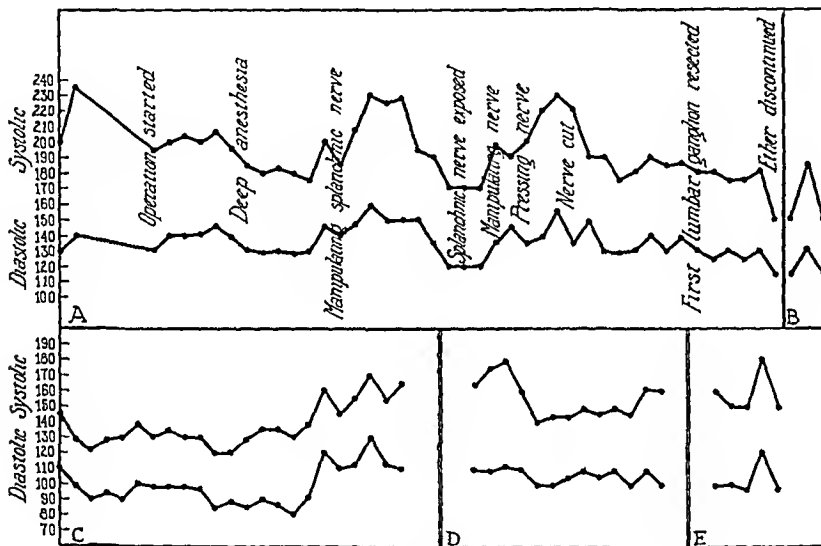


Fig 6—A, readings of blood pressure during resection of the left splanchnic nerves, B, cold test, C, pressures on the first day following the operation, D pressures two weeks after the operation, E, cold test

being more marked. The systolic pressure had been moderately labile. In the past few months the patient had had headaches in the morning, progressing dyspnea and general fatigue. The heart was enlarged to grade 2, and there were systolic murmurs in the apical and aortic regions. The specific gravity of the urine was lowered. The concentration of sulphates was 61 mg per hundred cubic centimeters of serum.

Before operation hourly readings of the blood pressure revealed a mean pressure of 200 systolic, with a range of from 160 to 220, and a mean diastolic pressure of 140, with a range of from 120 to 170. The cold test raised the blood pressure to 250 systolic and 170 diastolic, return to the previous level was delayed. The electrocardiogram gave evidence of an inverted T wave in lead III. The retinal arteries were narrowed, graded 2+, with sclerosis, graded 2, of the smaller branches, the retinitis was that of a severe form of hypertension (group 3). The patient could not tolerate spinal anesthesia, and preoperative studies were incomplete.

The right splanchnic nerves were resected on April 1, 1933. The sympathetic trunk was resected, and the first lumbar ganglion was removed. Right pneumothorax developed at the time of operation, and the patient was placed in an oxygen tent, the postoperative period otherwise was uneventful. The general condition was satisfactory, and the patient was dismissed from the hospital on April 17. She was kept under observation.

Twenty-four hours following operation the blood pressure averaged 210 systolic and 160 diastolic. At the time of dismissal the mean blood pressure for twenty-four hours was 220 systolic and 160 diastolic. The systolic pressure varied from 200 to 235, the diastolic pressure, from 150 to 170. Seventeen days after operation, when the patient was up and about, the mean pressure was 195 systolic and 140 diastolic. The response of the blood pressure to cold was unchanged. There were no demonstrable changes in the retinal arterioles.

Six weeks after operation, an infection developed in the upper part of the respiratory tract, from which the patient recovered. A pleural friction rub was noted at this time. The patient gained 8 pounds (3.6 Kg), and the general condition was excellent. She returned for reexamination on July 3. There were no symptoms except fatigue. In the interval following dismissal several infections of the upper part of the respiratory tract developed. The blood pressure was 235 systolic and 150 diastolic. Albumin, graded 3, and a few erythrocytes were present in the urine. The value for urea was 30 mg, and the return of phenolsulphonphthalein was 35 per cent. The value for sulphates was 8 mg. Examination of the ocular fundi revealed a few fresh hemorrhages and exudates.

On August 22 the blood pressure remained fairly constant (230 systolic and 150 diastolic). With the cold test the pressures were 250 systolic and 170 diastolic. There was a residual pleural rub over the base of the right lung. The retinal findings were unchanged. The patient had gained 14 pounds (6.4 Kg) and had no symptoms. Eight months after operation, her general course was progressively downward, with evidence of mild renal insufficiency. The blood pressures were unchanged.

Comment—The patient in case 3 had marked organic change in the retinal arteries and in the specimens of the arterioles removed for biopsy (fig 7). Following operation there was no reduction in the mean levels or in the response of the blood pressure to stimulation. There was definite stabilization of the blood pressure at rather high levels. Respiratory infection had a serious effect on the kidneys and retinal arteries. The blood pressure increased, the diastolic more than the systolic. The early renal insufficiency had a pressor action, nullifying the possible beneficial effects of the operation. The course of events in this case is similar to that in case 2. A prolonged period of rest and further observation will be carried out before resection of the left splanchnic nerves can be considered.

CASE 4—A man, aged 34, was first seen in 1921, at which time his blood pressure was normal and his complaints were not related to any form of cardiovascular disease. His second admission was on Dec 5, 1932, at which time he complained of fulness in the head, more evident in the morning on arising. He was excitable and emotional. With the headaches there was vertigo when he bent over or suddenly turned the body. Following moderate exertion there were definite

dyspnea and palpitation for short periods. The mean blood pressure was 200 systolic and 140 diastolic. Examination of the retinal vessels revealed sclerosis, graded 2, with extensive retinitis of a severe form of hypertension (group 3). The peripheral arteries were hypertrophied and tortuous. Urinalysis revealed the presence of albumin, graded 3, and a few hyaline casts. The value for sulphates was 42 mg, and the value for urea, 26 mg. The concentration of hemoglobin was normal, and there was no renal insufficiency. A specimen of muscle removed for biopsy revealed diffuse vascular disease (group 3). Latent glomerulonephritis was considered, but in view of the changes in the arterioles, it was felt that the renal findings were secondary to the nephrosclerosis.

The patient returned to the clinic on June 26, 1933, for reexamination. The symptoms had been practically unchanged except for increased mental irritability. Examination at this time revealed that the blood pressure varied from a basal

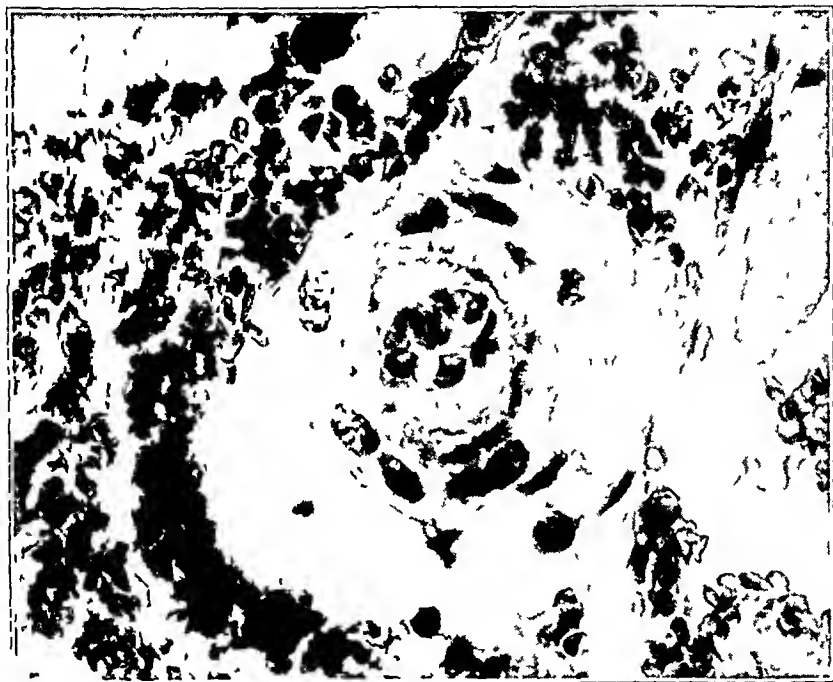


Fig 7—Organic changes in an arteriole

level of 208 systolic and 112 diastolic to 248 systolic and 150 diastolic. The retinitis was still active, and there was irregularly distributed sclerosis, graded 3, of the arterioles with venous dilatation and marked localized periarteritis and endarteritis of the left superior temporal arteriole, partial obliteration was present, and suggested an inflammatory element. There were slight blurring and mild edema of the margins of the disks. These changes indicated the development of a malignant form of hypertension. Urinalysis revealed albumin, graded 3, with fixation of the specific gravity, the value for urea was 38 mg, and that for sulphates was 52 mg. An electrocardiogram revealed an inverted T wave in lead I. Physical examination revealed no changes.

Keith and Horton felt that the patient had made some definite progress since his previous visit. The patient asked if operation on the sympathetic nerves would offer him any relief. Spinal anesthesia at the level of the nipple disclosed a residual blood pressure of 170 systolic and 130 diastolic.

In spite of the marked organic change in the vessels and the early renal insufficiency, the wishes of the patient were carried out in this matter, and on July 10 the left splanchnic nerves, twelfth thoracic ganglion and a portion of the sympathetic trunk were resected. Convalescence was uneventful. The pressor responses to cold may be noted in figure 8. There is considerable variability in the maximal levels obtained with stimulation by cold. Thirteen days after operation the patient was up and moderately active, at this time the mean blood pressures were 170 systolic and 120 diastolic. The general condition was satisfactory. The value for blood urea was 56 mg, and for serum sulphates, 6.8 mg. The patient was allowed to return home for several months before it was decided to resect the right splanchnic nerves. At the time of his dismissal, there was no significant change in the retina.

Comment—The patient in case 4 had a severe form of essential hypertension, with advanced medial hypertrophy of the arterioles and

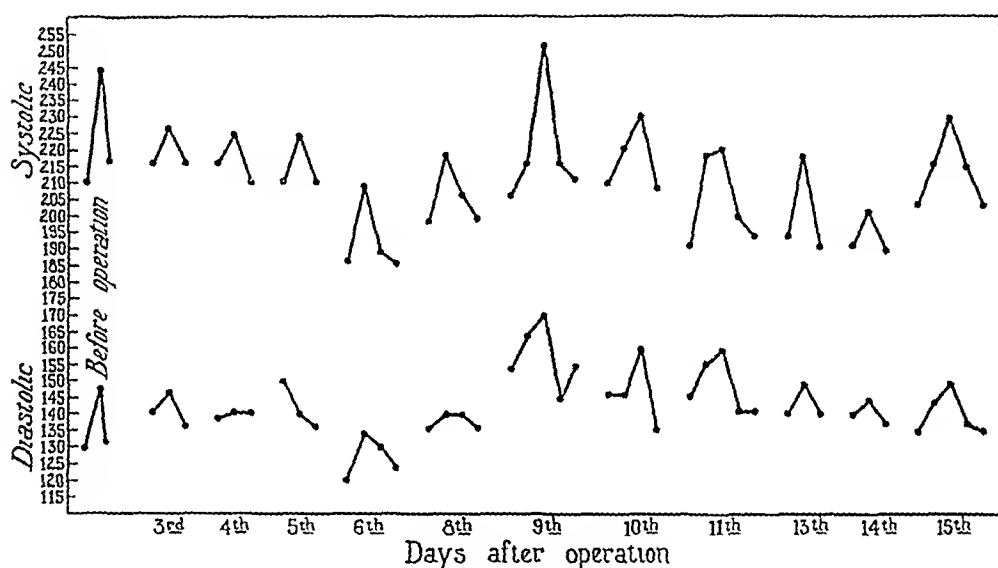


Fig 8 (case 4)—Pressor responses to cold

ophthalmoscopic evidence of early malignant hypertension. There was mild renal insufficiency, probably secondary to nephrosclerosis. The basal level of the blood pressure with rest, spinal anesthesia and general anesthesia was 130 diastolic. This patient had a form of hypertension which was not favorable to operation on the sympathetic nerves because of the degree of arteriolar hypertrophy and the added factor of early renal insufficiency, both of which affect the peripheral vasopressor mechanism. The operation was carried out largely at the patient's request, in view of the rather hopeless prognosis, he insisted that we try this procedure.

The response of the blood pressure following operation is of interest. The levels attained by stimulation with cold varied in striking degree, a variation not observed in repeated tests on hypertensive subjects (fig 8). This variability suggests a peripheral effect, probably from renal toxemia.

CASE 5—A woman, aged 32, did not know of any family history of hypertension. The complaints on admission were arthritis and diffuse neuromuscular pains. The patient was known to have had hypertension for at least eight years. The systolic blood pressure had been found to be as high as 190 and with rest as low as 144. The patient had had frequent attacks of vertigo associated with nausea, and there had been increased fatigue, exhaustion, nervousness and slight dyspnea.

The retinal arteries were found to be attenuated, with sclerosis of the hypertensive type graded 1. Definite hypertrophy of the heart could not be demonstrated. Urinalysis gave negative results. The value for urea was 22 mg. Hourly studies of the blood pressure under basal conditions revealed a range from 120 to 180 systolic and from 80 to 130 diastolic. The response of the blood pressure to stimulation by cold was 190 systolic and 130 diastolic, following inhalation of 10 per cent carbon dioxide the maximal response of the blood pressure was 195 systolic and 140 diastolic. The diagnosis was essential hypertension in the early organic stage, with marked fluctuations in the responses of the blood pressure to stimulation.

On Aug. 18, 1933, the left splanchnic nerves and the twelfth thoracic and first lumbar sympathetic ganglions were resected. A specimen of the lumbar muscles was removed for biopsy. The patient recovered promptly, she was up and about on the eighth day, and convalescence was uneventful. There was a reduction of

Studies of Temperature (Degrees Centigrade) of the Feet in Case 5

	Sole	1	2	3	4	5
Left	30.3	26.9	26.7	26.7	26.9	27.1
Right	34.7	32.5	33.8	34.1	34.3	34.4

approximately 20 in the systolic pressure reaction to stimulation with cold, and one week after operation the left foot was much warmer than the right. This vasodilatation gradually disappeared, and within two weeks the temperature of this foot reached that of the other.

On September 12 the right splanchnic nerves were resected and the lumbar sympathetic chain was divided, two ganglions were resected. Recovery from this operation was uneventful. The right foot became much warmer than the left, and this persisted until the patient's dismissal a month later. As no symptoms could be attributable directly to the hypertension, there was no particular change in the subjective sensations. The patient stated that there was perhaps slight increased laxity in the movements of the bowels, but there were no other untoward symptoms in the abdominal viscera.

The temperature of the toes one month after operation in degrees centigrade is given in the table.

There was complete absence of sweating of the right leg below the knee and of the left leg below the lower middle part.

Comment—The patient in case 5 had a fairly early form of essential hypertension, apparently it was just entering the organic phase. The blood pressure was remarkably labile and fluctuated within wide limits. Biopsy, obtained at the time of the first operation revealed questionable thickening of the muscular coat of the arterioles. It is obvious from studies of the blood pressure that the response to the bilateral operation

was not marked. Sharp increases in the patient's blood pressure could be induced with a standard stimulus (cold), but at a somewhat reduced level. The vasodilatation of the feet was incomplete in the left leg and probably complete in the right leg. It persisted for thirty days following the operation on the right side. So far as is known, the same ganglions were removed, the twelfth thoracic and first lumbar. Sweating tests gave further confirmation of incomplete removal of the sympathetic fibers on the left side and complete removal on the right.

THE EFFECTS OF THE OPERATION ON BLOOD PRESSURE

It is difficult to make comparisons of the changes in blood pressure of different subjects because of the differences in the severity of the hypertension. In addition, general anesthesia and the prolonged rest following operation usually lower the levels of blood pressure. For that reason comparison of the preoperative and postoperative readings of blood pressure was considered valid after the patient had resumed activity. Of greater import in our opinion in evaluating the effects of operation has been comparison of the pressor responses of the blood pressure to cold and psychic stimulation.

In case 1 a quantitative effect was demonstrable on the retinal arterioles. Following bilateral resection of the splanchnic nerves, the depressor effects were not significant. For several months following the operation on the left side, the levels of blood pressure were lower, and there was diminished lability in the hourly readings. The course of the hypertension was seriously affected by an intercurrent infection and by the development of renal insufficiency, which led to the patient's death six months later. We believe that the renal condition nullified to a large degree the possible depressor effects of the operation. This patient had the most severe form of hypertension of any patient in this series and the greatest degree of organic change in the arterioles. The effects of changes in posture on the blood pressure were not decisive. No significant lowering of the systolic pressure was obtained in the upright position.

In case 2, in which the left splanchnic nerves were resected, there was moderate reduction in the responses and mean levels of the blood pressure, and these continued to be below the preoperative levels. The hourly fluctuations in the readings of blood pressure were sharply diminished.

In case 3, following resection of the right splanchnic nerves, the only significant effect on the blood pressure was a tendency toward stabilization, but the mean levels, if anything, were higher. Again, an intercurrent infection, which was contracted a month after operation and which was causing renal injury, may have excited pressor effects.

In case 4, following resection of the left splanchnic nerves, the proper reactions to cold were inconstant and variable, a condition not observed in repeated tests on hypertensive subjects. The mean levels were not affected.

In case 5, a fairly early form of hypertension, with marked lability and exaggerated pressor reactions, was noted. Bilateral resection of the splanchnic nerves was followed by a moderate reduction in the height of the pressor responses.

THE POSSIBLE EXPLANATION OF THE LACK OF EFFECT ON THE BLOOD PRESSURE

If significant effects on the blood pressure are not obtained after bilateral resection of the splanchnic nerves, the following explanations seem valid. 1 The splanchnic arteries are not completely denervated. A few preganglionic fibers descend by way of the aorta and are not removed by the operation. In addition, there are some fibers which contribute to the splanchnic innervation from the lower lumbar ganglia, the number and significance of these nerves in man are not known. Cannon¹⁶ stated that in animals they are present in considerable numbers. 2 The vasomotor nerves of the arterioles of the thorax and the upper and lower extremities, which remain after the splanchnic nerves are removed, are sufficient to cause a general vasopressor effect. This seems unlikely, as cervicothoracic and lumbar sympathetic ganglionectomy do not produce significant depressor effects. 3 The organic hypertrophy in the arterioles is too advanced, superimposing a peripheral factor on the central vasopressor control. 4 If renal insufficiency is present, it is likely again that the peripheral mechanism is disturbed, superimposing an added pressor element.

SYMPTOMATIC EFFECTS OF RESECTION OF SPLANCHNIC NERVES

The clinical effects of the operation depend largely on the symptoms attributable to hypertension that existed before operation. In case 1 relief of the patient's headaches was temporary, and their recurrence could be attributed to the subsequent development of renal insufficiency. In case 2 the patient's headaches and vertigo were entirely relieved. In case 3 there were no symptoms that could be attributed directly to the hypertension, in spite of the fact that the patient had a severe form of hypertension. In case 4 the symptoms were those of cerebral instability, and evaluation of symptomatic effects was difficult. In case 5 the patient had no symptoms which could be attributed to the hypertension.

16 Cannon, Bradford. The Effects of Progressive Sympathectomy on Blood Pressure, *Am J Physiol* **97** 592 (July) 1931.

COMMENT

The problem of selection of patients for operation is crucial. It is more complex than the selection for sympathetic ganglionectomy of patients with occlusive diseases of the peripheral arteries. In treating a given patient with hypertension, it is desirable to determine preoperatively the probable effects on levels and responses of blood pressure by temporarily blocking the splanchnic nerves.

Under spinal anesthesia to the level of the nipples, small doses of from 60 to 80 mg of procaine hydrochloride being used, the blood pressure was lowered, and the vasopressor responses of the patients were greatly diminished or obliterated. The abolition of the pressor reactions by this procedure indicates the neurogenic mediation of these reactions. Untoward effects of lowering of the blood pressure are not noted. Spinal anesthesia not only anesthetizes the splanchnic nerves but the lower sympathetic chain and the motor and sensory nerves to the lower extremities and abdominal wall. With spinal anesthesia to levels as high as the nipple, a greater number, and additional types, of nerves are blocked than are blocked by splanchnic sympathectomy.

The degree of organic hypertrophy of the musculature of the arterioles is of great importance in predicting the probable postoperative depressor effects. This can be determined by careful examination of the retinal arterioles and by noting the presence or absence of spastic phenomena. Pathologic study of arterioles of specimens of muscle removed for biopsy gives decisive information as to organic grading and prognostic information. It must be recognized, however, that the degree of changes in the arterioles is not uniform throughout the body, and a too exact deduction cannot be made from the changes in one group of arterioles. We are of the opinion that the following criteria are useful in determining suitability for operation in a case of hypertension. The subject should be less than 45 years of age, the levels and responses in blood pressure should be markedly variable, changes in the smaller arterioles should not be advanced, and severe, degenerative changes should not be present in the kidneys, heart or brain. The foregoing constitute the major requisites for this operation. A basal level of the diastolic blood pressure of not more than 120 is desirable.

Essential hypertension is assumed to be the result primarily of (1) a hyperreactive vasomotor center with exaggerated pressor responses from psychic, sensory, chemical or hormonal stimulation, (2) consecutive to these excessive, rapidly varying intra-arterial stresses, organic hypertrophy of the arterioles is induced, and (3) in the more advanced stages renal sclerosis and associated vasospastic reactions superimpose an added and more serious element. The two last mentioned conditions are believed to be peripheral, the former, central. Operative measures

which block the central mechanism from the splanchnic circulation should theoretically be effective in the absence of a gravely disturbed peripheral mechanism

This concept of the various stages in essential hypertension is useful in the interpretation of postoperative results. It emphasizes in which stage of the disease the most striking improvement from operation should be obtained.

Untoward Effects—There was no significant disturbance of the function of the abdominal viscera that could be attributed to unilateral or bilateral section of the splanchnic nerves. In case 1 severe constipation developed following the second operation. In case 2 there was slight weakness of the right abdominal muscles with a small area of anesthesia in the right lower abdominal quadrant. More exact studies should be carried out on the function of the gastro-intestinal system and especially the effect on renal function following the unilateral operation.

SUMMARY

Five patients with essential hypertension of varying degrees of severity have been subjected to unilateral or bilateral resection of the splanchnic nerves and to removal of the first lumbar ganglion. In two subjects, significant quantitative reduction of the pressor reactions to cold resulted. In one subject, subjective and objective improvement was striking. In the most severe forms of essential hypertension, with early renal involvement and advanced organic changes in the arterioles, the effects on the blood pressure have not been striking. Resection of the splanchnic nerves is a relatively safe operation and carries small risk. No untoward effects have been noted. Further application of this surgical procedure is justifiable in the early stages of the severe progressive form of essential hypertension in young persons.

ALLERGIC DEATH

VII PROTRACTED SHOCK

GEORGE L WALDBOTT, M D

DETROIT

Reference has been made recently in the literature to instances of sudden death which were thought to be due to physical allergy, particularly to sensitization to cold (Tannhauser,¹ Grassl²) Few, if any, reports of allergic deaths induced by the antigenic substances which are commonly encountered in allergic diseases can be found, except deaths which followed parenteral injections of pollen and serum³

Yet the possibility of such deaths is strongly suggested because of the relative frequency and severity of nonfatal generalized reactions following contact with, or the inhalation or ingestion of, antigens, particularly in allergic children Duke,⁴ for instance, described the case of a man who was so sensitive to fish glue that licking a postage stamp produced a severe generalized reaction He recorded other incidents of similar reactions following skin testing by the scratch method I have recorded⁵ similar observations from both my own experience and that of others

Evidence has been presented⁶ that cases of so-called "thymic death" manifest pathologic changes which appear to be identical with those of allergic shock⁷ An attempt is made here to substantiate the theory of this identity by enlarging on a condition which is frequently encountered in such cases, namely, the occurrence of bronchopneumonic lesions

1 Tannhauser, S J Zur Frage des Badetodes, Munchen med Wchnschr **79**.1890, 1932

2 Grassl Zur Frage des Badetodes, Munchen med Wchnschr **79** 1469, 1932

3 Waldbott, G L (a) Systemic Reactions from Pollen Injections, J A M A **96** 1848 (May 30) 1931, (b) The Prevention of Anaphylactic Shock, *ibid* **98** 446 (Feb 6) 1932

4 Duke, W W Asthma, Hay Fever, Urticaria and Allied Manifestations, St Louis, C V Mosby Company, 1926

5 Waldbott, G L, and Anthony, G E So-Called Thymic Hyperplasia IV A Follow-Up Study of Thirty Cases, Am J Dis Child **47** 34 (Jan) 1934

6 Waldbott, G L So-Called "Thymic Death" VI The Pathologic Process in Thirty-Four Cases, Am J Dis Child **47** 41 (Jan) 1934

7 The term "anaphylactic shock" appears to be more appropriate because the evidence for a distinction of allergic from anaphylactic shock is not conclusive However, in order to avoid confusion, I am adhering to the terminology of Coca which is accepted at present by most writers

EXPERIMENTAL EVIDENCE

The phenomenon of "protracted" anaphylactic shock in animals is well known to immunologists. Its manifestations were described by Dean and Webb,⁸ who found in their experiments with anaphylaxis in dogs that in the more severe cases of shock which did not terminate fatally there "is another train of symptoms" after the acute state has subsided. This is characterized by dyspnea, fever, diarrhea, stupor, vomiting and general malaise. In guinea-pigs a similar picture was produced by Ratner and his co-workers⁹ by means of continued exposure to the antigenic substances after the production of shock. Other workers (Ishiooka,¹⁰ Busson,¹¹ Friedberger,¹² Fried¹³) have spoken of "sterile anaphylactic pneumonia" which occurs in guinea-pigs sensitized to horse serum on insufflation or inhalation of horse serum into the trachea. The lesions which are thus produced may offer the clinical picture of interstitial bronchopneumonia or they may involve whole lobes. Hemorrhagic infarctions of various sizes were noticed among the inflammatory lesions. The aseptic character of the lesions and the presence of lymphocytes and of emphysema are additional features which suggested a pathologic differentiation from true pneumonia.

In man, I have encountered a syndrome corresponding closely with that of protracted anaphylactic shock on three different occasions: first, following injections of antigen, second, in cases of severe asthma, and third, among patients who died of what had been termed "thymic death."

REPORT OF CASES

1 *Protracted Allergic Shock Following Injections*—CASE 1—M. B., a 7 year old girl with asthma who was sensitive to various foods, pollen and epidermal allergens was given 0.1 cc of a 1:100 solution of cotton-seed extract for the purpose of hyposensitization. Within three minutes an area of local edema, the size of an apple, occurred at the site of the injection. This was soon followed by generalized urticaria, edema and severe wheezing. From 0.5 to 1 cc of epinephrine was given every half hour to an hour to control the reaction. The wheezing and urticaria were held in check for some time, but the child's condition

8 Dean, H. R., and Webb, R. A. The Morbid Anatomy and Histology of Anaphylaxis in the Dog, *J. Path. & Bact.* **27** 5, 1924.

9 Ratner, B., Jackson, H. C., and Gruel, H. L. Respiratory Anaphylaxis: Sensitization, Shock, Bronchial Asthma and Death Induced in the Guinea-Pig by Nasal Inhalation of Dry Horse Dander, *Am. J. Dis. Child.* **34** 23 (July) 1927.

10 Ishiooka, S. The Histology of Anaphylactic Pneumonia, *Deutsches Arch. f. klin. Med.* **107** 500, 1912.

11 Busson, B. Protein Anaphylaxis Induced Through the Respiratory Passages, *Wien. klin. Wchnschr.* **24** 1492, 1911.

12 Friedberger, E. Ueber Anaphylaxie, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **8** 239, 1910.

13 Fried, B. M. Allergic Lobar Pneumonia (Experimental Study), *J. Exper. Med.* **57** 111, 1933.

warranted hospitalization for the balance of the day. When discharged twenty hours after the injection, she was practically free from symptoms. As soon as she returned home, severe wheezing started again, and was followed within a half hour by fever and cyanosis. At that time the chest showed areas of consolidation, bronchial breathing and râles alternating with rhonchi. The temperature ranged between 101 and 103.5 F. This lasted for three days. The removal of a cotton blanket from the child's bed resulted in decided relief from the wheezing. After the symptoms had entirely subsided the patient was retested by the scratch method and by passive transfer for cotton to which she had given a 4 plus reaction before. The skin tests gave a negative reaction at first, changing to a positive reaction seven days later.

CASE 2—Miss A. M., 18 years old, who had pollen hay fever complicated by clinical sensitivity to horse hair, was given 0.1 cc. of a 1:1,000 solution of horse hair extract as an intradermal test. Within five minutes a marked wheal and local swelling occurred, followed immediately by a generalized reaction. The patient was observed in the office for four hours, during which time she was given small doses of epinephrine. She was relieved for approximately eight hours, then she retired to her bed on which there was a mattress made of horse hair. Immediately a cough and wheezing developed, soon followed by fever, râles and impairment of the percussion note in the chest. On removal of the mattress the wheezing subsided, but the fever, ranging from 100 to 102.5 F., persisted for two more days.

Comment—In these two cases of severe allergic shock, the symptoms did not subside in the usual way, but were followed by a condition resembling low grade bronchopneumonia. The continued contact with the causative antigen undoubtedly aggravated the condition in a manner similar to that demonstrated in the experiments of Ratnei and his associates. Its removal tended to counteract the symptoms of shock, but did not influence the secondary infection. It is noteworthy that negative skin reactions were encountered soon after the shock, in spite of definite previous sensitivity. This corroborates previous observations on skin tests following shock from substances other than pollen and serum (Waldbott¹⁴). Walzer¹⁵ also recorded negative reactions to skin tests and passive transfer tests in a case of shock following an injection of horse serum.

CASE 3—M. H., a 12 year old colored girl, was given 0.2 cc. of typhoid vaccine intravenously as treatment for iridocyclitis, on April 6, 1933. There was a history of asthma in the child's family. About four hours after the injection fever, dyspnea and cough developed, followed by unconsciousness and involuntary urination and bowel movements. The temperature was 103 F., the pulse rate 110 and the respiratory rate 30. On the following day the physical signs of bronchopneumonia in both lungs were detected. On the third day following the injection the child died.

14 Waldbott, G. L., Allergic Shock from Substances Other Than Pollen and Serum, *Ann Int Med* 7 1308 (April) 1934.

15 Walzer, M., New Diagnostic Methods in Asthma, *Long Island M. J.* 60 85, 1932.

The autopsy (Dr W R Prentice, Kalamazoo, Mich) revealed, on gross examination, slight congestion and edema of the cerebral and meningeal blood vessels and a few petechial hemorrhages in the cerebellum. There were areas of solidification in both lungs, other sections showed extreme congestion and still others marked emphysema. The spleen was enlarged (422 Gm). There were numerous enlarged lymph nodes, particularly in the gastro-intestinal tract and cervical region. The thymus weighed 22.5 Gm. Otherwise no noteworthy pathologic changes were found. On microscopic examination the brain showed slight congestion, and the lungs were patchy with early bronchopneumonia, with massive intra-alveolar hemorrhages and edema, necrosis of the alveolar epithelium and marked emphysema. There was some cloudy swelling of the hepatic cells with marked congestion in the capsule of Glisson. The thymus, spleen and other lymph nodes were markedly congested and the lymph tissue hyperplastic.

Comment—While the theory of allergic death caused by a bacterial vaccine may not be fully in accord with the conception of shock from nonbacterial antigens, this case is reported here because the pathologic changes seemed to correspond fully with those reported observed in sensitized animals following injections or inhalation of nonbacterial antigens, and also with my observations at autopsy following "thymic death." Furthermore, the family history in this case suggested that the patient was probably allergic.

I have had occasion to study two other cases of death following intravenous injections of typhoid vaccine which showed the identical clinical course and pathologic changes.

2 Prolonged Shock in Persons with Asthma—In a recent paper Clarke¹⁶ described a type of asthma characterized by unusual severity. He mentioned as its symptoms extreme prostration, coma, râles in the lungs and fever. His patients did not improve with the administration of epinephrine. Clarke stated that this condition occurred in few of his patients with asthma. I have encountered this condition in several cases, but in only two was I able to record the full sequence of events.

CASE 4—Mrs J C, 31 years old, had attacks of severe asthma for four years at intervals of three or four months. When she spoke of the attacks she expressed extreme fear, much more than I have seen in any other patient. She had a feeling of impending death. The skin tests showed from 2 to 3 plus reactions to various foods, ragweed, timothy and red top grass, chicken feathers and hair from dogs and cattle. The patient was treated with injections of extracts of chicken feathers and ragweed and autogenous vaccine, from October 1931 to November 1932, during which time she had one slight attack of asthma. In November 1932, a few minutes after she had contact with a dog, a severe attack developed which necessitated hospitalization. There were profuse sweating, a pulse rate of over 140, coma and dyspnea. Numerous râles were heard in various parts of the chest, areas of impairment alternating with areas of hyper-resonance. The heart sounds were faint, no murmur was heard. The blood

16 Clarke, J A. Status Asthmaticus or Subacute Asthma, J Allergy 4 481 (Nov) 1933

pressure ranged about the level of 95 systolic and 50 diastolic. There was expectoration of large quantities of sputum which occasionally showed a bloody tinge. Epinephrine in doses of from 0.5 to 0.75 cc was of no avail. On the third day the temperature began to rise to about 102° F, as indicated in figure 1. The blood count showed 11,000 white blood cells, with 68 per cent neutrophils, 32 per cent lymphocytes and no eosinophils. During the following days large quantities of thin clear sputum were expectorated. The patient regained consciousness, and the condition in the chest cleared up rapidly. Skin tests done at that time gave negative results, but when repeated two weeks later they showed reactions similar to those previously noted, including a 3 plus reaction to dog hair.

CASE 5—Mrs. L. K., a 27 year old woman, with severe asthma, who was sensitive to various antigens, took during an interval when free from asthma a patent medicine containing sodium salicylate for the relief of headache. She knew that she was sensitive to this drug, but did not know that it was contained in the medicine. Within a minute she became short of breath. She had scarcely given herself 0.5 cc of epinephrine when she lost consciousness. One hour later she

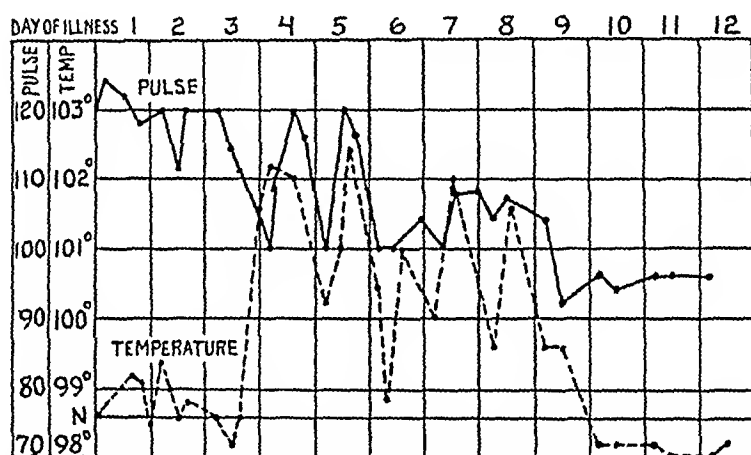


Fig. 1 (case 4) —Pulse and temperature curve in protracted allergic shock

was found on the floor wheezing severely, comatose and in collapse. She was taken to the hospital where epinephrine was given in frequent doses, but there was no decided improvement. After about six hours fever developed, and blood-tinged sputum was expectorated. There was evidence of pulmonary edema and of a bronchopneumonic process. The patient was treated with epinephrine, digifolin and intravenous injections of dextrose solution, without noticeable response. On the fourth day, the fever, which had not exceeded 102° F, subsided and the patient improved rapidly.

Comment—The condition in cases 4 and 5 was distinct from bronchial asthma, because there was evidence of pulmonary edema and an ensuing pneumonic process in the lungs. That the edema was not of cardiac origin was evident from the absence of other signs of myocardial insufficiency and from the subsequent absence of cardiac changes. The pulmonary infection, on the other hand, is distinctly different from primary pneumonia because of the unusual onset and course. Both patients were allergic. The onset of the syndrome was definitely

linked with the ingestion of a drug and the contact with a substance to which the patients were sensitive

3 *So-Called "Thymic Death"*—The noteworthy pathologic changes in the thirty-six cases of so-called "thymic death" referred to in a previous report⁶ consisted of capillary congestion, exudation of edematous fluid and extravasation of blood cells into the alveolar tissue, areas of atelectasis alternating with emphysema, petechial hemorrhages, edema in various organs other than the lungs, eosinophilia and hypoplasia of the suprarenal medulla

In seven of the thirty-six cases and in three additional cases which I have subsequently investigated, in which bronchopneumonia ensued several hours or days after the onset, the clinical course of the disease paralleled closely that encountered in those previously described. In the following two cases the onset of the symptoms was definitely linked with the taking of certain foods

CASE 6—S L, a boy, 1 year old, had been in perfect health except for frequent afebrile nasal catarrh (allergic?). No family history was obtainable, because the child was a foundling. About one week before death he had an afebrile catarrh of the upper respiratory tract from which he recovered within several days. On the morning of the day of death he seemed playful and in good health. The temperature was normal. At 10 o'clock, while drinking a glass of milk, he suddenly became cyanotic and dyspneic and vomited. The cyanosis and dyspnea increased, moist râles were noted in the lungs and signs of consolidation developed. At 3 p. m. the temperature was about 103 F, and at 6 p. m. the child died. The postmortem examination (Dr. L. Parker, Kalamazoo, Mich.) revealed a thymus gland weighing 40 Gm, hyperplasia of the bronchial and mediastinal lymph nodes, dilatation of the capillaries in the lungs, exudation of fluid into the alveoli with extravasation of blood cells, small areas of bronchopneumonic infiltration and areas of emphysema alternating with atelectasis. There was some congestion of the spleen and kidneys. The suprarenal glands were not examined. Other organs, including the heart, were normal.

CASE 7—L S, a 3 month old infant of an allergic mother, showed frequent difficulties of respiration and afebrile nasal catarrh. It was noted that when he was given orange juice, he showed severe dyspnea. When 2 months old, he was given a therapeutic dose of roentgen rays because of roentgenographic evidence "of an increased width of the upper mediastinal shadow with a slight lateral deviation of the trachea." One month later after taking some orange juice, the baby became "extremely pale" and dyspneic during his sleep. The father, a physician, noticed râles throughout both lungs. Within a few hours fever developed and the temperature rose to 104 F. Four hours subsequently the baby died. The autopsy revealed marked capillary congestion and edema, areas of mononuclear and neutrophilic infiltration in the lungs, eosinophilia in the spleen, edema in the leptomeninges and petechial hemorrhages in the peritoneum. The weight of the thymic gland was 15 Gm. The lingual and hilar lymph glands were considerably enlarged. The heart was normal.

Comment—In case 6, unless one considers as a cause of death a mechanical asphyxiation by food which entered the trachea (which

would have been easily detectable at autopsy), one is inclined to assume sensitization to milk as the causative agent, in view of the history of frequent afebrile "colds" which may have been allergic. In case 7, there was a typical history of sensitization to orange juice with a family history of allergy. The syndrome began after the ingestion of orange juice. In both cases a low grade pulmonary infection preceded death.

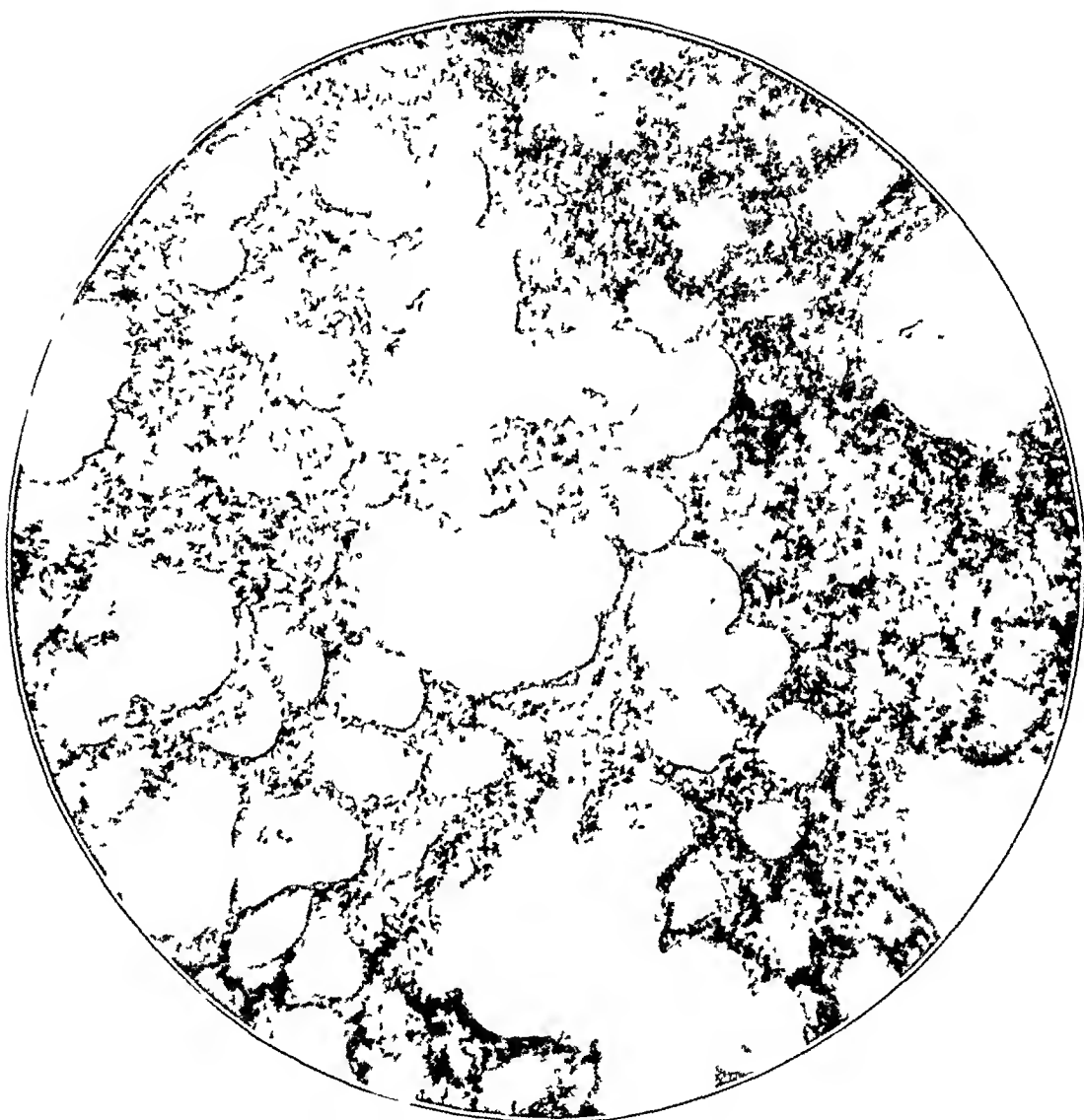


Fig 2 (case 3) —Photomicrograph of lungs demonstrating hemorrhagic areas

INTERPRETATION OF OBSERVATIONS

Allergic shock is the result of absorption of an excessive overdose of antigen to which a person is sensitive.^{7b} In cases 1, 2, 4 and 5, there is no doubt as to this mode of the reaction. In cases 3, 6 and 7, the allergic background, the course of the clinical manifestations and the parallelism in the pathologic findings with that of allergic shock, on which I have enlarged elsewhere,⁶ make it probable that this condition is identical with that of the other cases.

The fever encountered can probably best be explained on the basis of the primary pulmonary edematous hemorrhagic lesions which become infected or infiltrated with cellular elements in an attempt of the organism to organize these lesions. Whether or not bacterial infection plays an essential part in the production of the pneumonic lesions is difficult to say. In view of the presence of edematous hemorrhagic

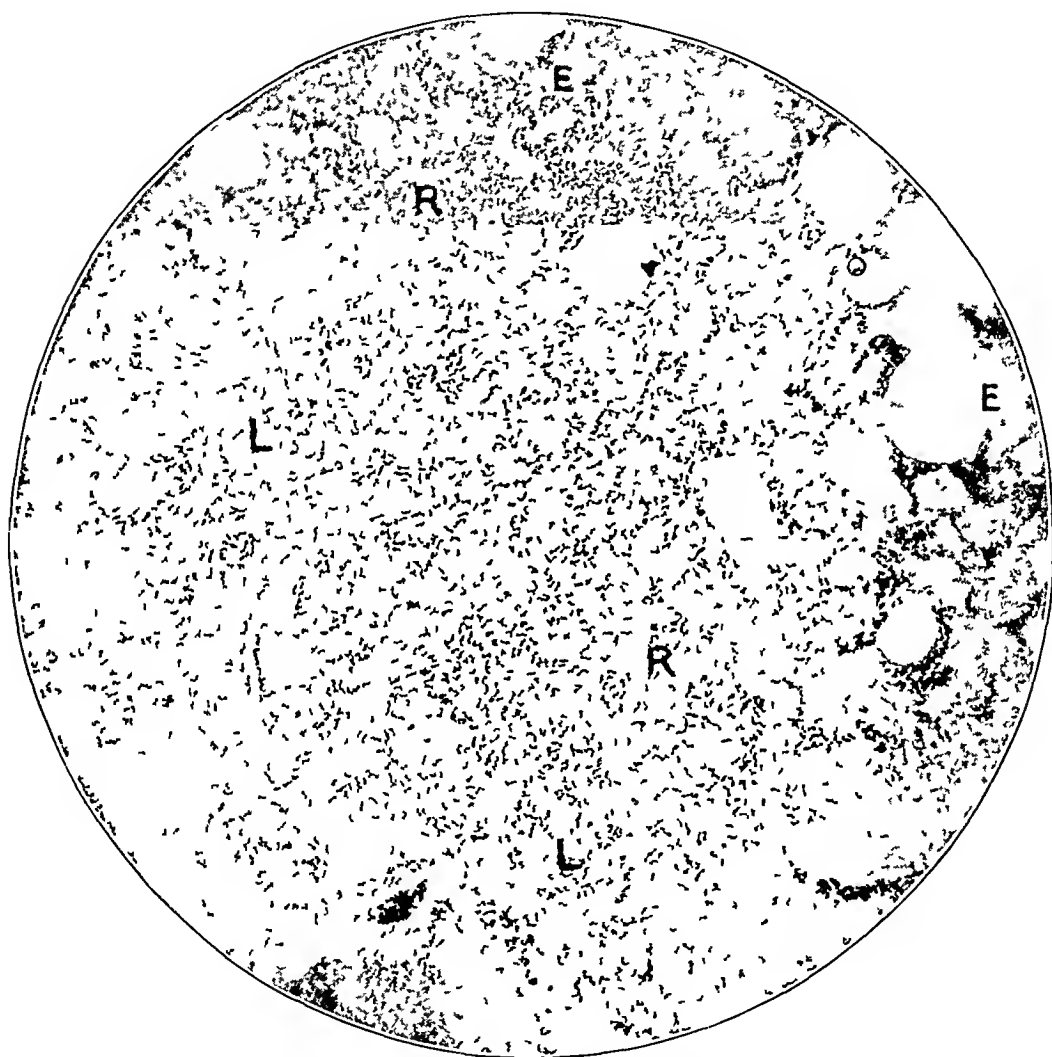


Fig 3 (case 6) —Photomicrograph of lung demonstrating a hemorrhagic lesion with an adjoining infectious process, *E*, edematous areas, *R*, extravasation of red blood cells, and *L*, leukocytic infiltration

lesions in the accelerated type of shock, it is likely that in the cases in which bacteria are detected in the blood stream or in the sections of the lungs, one is dealing with secondary infection. Moreover, in most of the tissues examined the infected areas surround the hemorrhagic edematous lesions (fig 2), which indicates a tendency of the organism to dispose of the primary hemorrhagic lesions.

Of interest in this connection is the case reported by MacDermot¹⁷ of an asthmatic person who had an injection of horse serum and who died several days later. The autopsy showed intra-alveolar hemorrhages, edema and bronchopneumonic areas. MacDermot interpreted the condition as being caused by anaphylactic shock. His microscopic sections, which I had the privilege of examining, show a remarkable resemblance to lesions noted in the cases reported here, particularly to those of case 3.

SUMMARY

The symptom complex of protracted allergic shock is described. It is characterized by a sudden onset of wheezing, dyspnea, shock and the physical findings of pulmonary edema, which is followed after several hours by the development of low grade bronchopneumonia. This has been observed following injections of an overdose of antigen in sensitive persons, in patients with severe asthma following contact with antigens toward which marked sensitivity exists and in ten of thirty-nine cases of so-called "thymic death" which came to autopsy. The detailed reports of two such cases are presented, in which sensitization to food appeared to be instrumental in causing death. The outstanding anatomic changes were edematous hemorrhagic lesions, the border of which showed infectious processes resembling bronchopneumonia.

10 Peterboro Street

17 MacDermot, H. E. Pulmonary Intra-Alveolar Hemorrhage in Case of Asthma Associated with Pneumonia, *Canad. M. A. J.* **22**: 533 (April) 1930.

LYMPHEDEMA OF THE EXTREMITIES
CLASSIFICATION, ETIOLOGY AND DIFFERENTIAL DIAGNOSIS
A STUDY OF THREE HUNDRED CASES

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General information about lymphedema tends to be somewhat confused and vague, in spite of a considerable number of excellent reports that may be found in medical literature. This situation is due in large part to the relative rarity of lymphedema, to an inadequate knowledge of its etiology, bacteriology and pathology and to the absence of a comprehensive classification. Although it is impossible for any single author to clarify all these shortcomings, I feel that a presentation of the pertinent data from the records of three hundred cases observed at the Mayo Clinic in the previous ten years offers an opportunity to fill many of the gaps in knowledge and to present a more or less orderly and logical pattern of classification, etiology and description of the condition. Aids to such a presentation are furnished by recent excellent work on the anatomy and physiology of lymph and lymph vessels, well illustrated by a monograph by Drinker and Fields¹. These facts regarding the anatomy and physiology of lymph vessels and lymph are so important for an understanding of lymphedema that it seems advisable to review them briefly.

DEFINITION OF TERMS

Lymph is a fluid obtained from lymph vessels. Tissue fluid is that found in the region outside blood and lymph capillaries in the cellular interspace. Plasma is the unclotted fluid of the blood. Lymphedema is a swelling of soft tissues due to an increased quantity of lymph. Elephantiasis, an advanced stage of lymphedema, is a "progressive histopathologic state characterized by a chronic inflammatory fibromatosis or hypertrophy of the hypodermal and dermal connective tissue"².

ANATOMY

Lymph vessels either are modified veins or arise in situ from mesenchymal cells. They are closed vessels which possess an unbroken endo-

From the Division of Medicine, the Mayo Clinic

1 Drinker, C K, and Fields, Madeleine E. Lymphatics, Lymph and Tissue Fluid, Baltimore, Williams & Wilkins Company, 1933, p 254

2 Matas, R. The Surgical Treatment of Elephantiasis and Elephantoid States, Dependent On Chronic Obstruction of the Lymphatic and Venous Channels, Am J Trop Dis 1 60, 1913

thelial lining, bathed on the outside by tissue fluid. In general, there is more lymphatic than hematic capillary surface. Every main blood vessel has an accompanying lymph vessel.³ The lymph vessels are as richly supplied with valves as are the veins.⁴ India ink injected between two ligatures into the lumen of an artery appears in the lymph vessels around the artery by passing through intracellular stomas and directly through the cells of the arterial wall.⁵

There are a superficial and a deep system of lymph vessels in the leg, but there is no communication between them except through the popliteal and inguinal lymph nodes.⁶ In animals most of the superficial lymph vessels of the leg and foot, as well as some of the deep lymph vessels that drain the muscles of the leg, terminate in the popliteal lymph node. From this node large efferent trunks course along the femoral vessels to end in the external iliac nodes, just distal to the bifurcation of the aorta. Many of the superficial lymph vessels of the thigh and upper part of the leg drain into the inguinal lymph nodes, which in turn have efferent vessels terminating in the external iliac nodes. The deeper lymph vessels in the muscle sheaths of the thigh eventually enter trunks that accompany the main femoral lymph vessels, and drain into the large iliac nodes.⁷ All the lymph vessels of the leg, both superficial and deep, join at the groin and pass along the external and common iliac vessels through the iliac nodes. The lymphatic trunks at the root of the leg hug the veins closely, and may even be embedded in the adventitia of their walls. They are enclosed in a tough fibrous sheath along with the great blood vessels.⁸

The superficial lymph vessels of the third, fourth and fifth fingers pass to the dorsum of the digits, then upward and around the ulnar side of the forearm to the flexor side of the forearm, where they join those coming from the entire ulnar side of the forearm and pass upward into the axillary nodes, with or without intervention of the cubital lymph node. Those of the index finger and thumb pass upward on the dorsum of these digits, then around the radial side of the forearm to the flexor

3 Polonskaja, R. Zur Frage der Klappen in den Lymphgefäßen der unteren Extremitäten des Menschen, *Anat Anz* **74** 395 (Sept 30) 1932

4 Funaoka, Seigo. Der Mechanismus der Lymphbewegung, *Arb a d dritten Abt d anat Inst d kaiserl Univ Kyoto* (ser D) **1** 1, 1930

5 Iwanow, G. Die Lymphgefäße der Wände der Blutegefäße—Vasa Lymphatica vasorum sanguinorum, *Ztschr f Anat u Entwicklungsgesch* **99** 669, 1933

6 Trout, H. H. Ulcers Due to Varicose Veins and Lymphatic Blockage, a New Principle in Treatment, *Arch Surg* **18** 2281 (June) 1929

7 Reichert, F. L. The Regeneration of Lymphatics, *Arch Surg* **13** 871 (Dec) 1926

8 Homans, John. Phlegmasia Alba Dolens and the Relation of the Lymphatics to Thrombophlebitis, *Am Heart J* **7** 415 (April) 1932

surface, where they join those coming from the radial side of the forearm, and pass upward to the axillary nodes. An occasional lymph vessel may pass upward on the extensor surface of the forearm to well above the elbow, where it turns sharply around the ulnar side of the arm to its inner side and thence to the axillary nodes. The superficial lymph vessels of the arm empty into the axillary nodes or, much less frequently, into the deltoideopectoral or supraclavicular nodes. The deep lymph vessels of the arm run with the large vessels to empty into the axillary lymph nodes, with or without the intervention of the deep cubital lymph nodes. The superficial and deep lymph vessels are connected at the elbow by the deep and superficial cubital lymph nodes.⁹

Regeneration and Collateral Circulation—If a large lymph vessel is cut, the circulation is carried on by collateral vessels. Later, the passage between the two cut ends regenerates, and the collateral circulation recedes. Collateral lymph vessels develop a few days after ligation of the main trunks.¹⁰ Regeneration of lymph vessels is rapid. They cross the scar of an incision as early as the fourth day, and by the eighth day regeneration is physiologically adequate.¹¹

PHYSIOLOGY

The lymphatic endothelium is more permeable than that of hematic capillaries. It possesses no selective absorptive power, but merely admits material forced on its outer surface. Particles of microscopic dimensions deposited in various parts of the body cannot move far except by entering and passing along the lymph vessels.

Pressure and Circulation of Peripheral Lymph—In amphibians, reptiles and some birds the lymph heart is very important for the movement of lymph. This organ is lacking in mammals. Although the media of the wall of the thoracic duct of man is made up of circular, smooth muscle fibers interlaced with collagen and elastic connective tissue, and although peripheral lymph vessels may have more or less smooth muscle fibers in their walls, it has not been demonstrated that these muscular elements have much to do with the movement of lymph. Active or passive contraction of skeletal muscles plays the most important part in the movement of lymph, the valves of the lymph vessels serve as the most important accessory arrangement for moving lymph forward.⁴

9 Bartels, Paul. *Das Lymphgefäß-System*, Jena, Gustav Fischer, 1909, p 280.

10 Funaoka, Seigo, and Skirakawa, Shigekiyo. Ueber die Entstehung der kollateralen Lymphbahnen nach Ausschaltung des Stammstroms, *Arch Anat Hist Nat* 15, 1930.

11 Reichert, F. L. The Recognition of Elephantiasis and Elephantoid Conditions by Soft Tissue Roentgenograms, With a Report on the Problem of Experimental Lymphedema, *Arch Surg* 20 543, (April) 1930.

The speed of circulation of lymph is rapid, but it varies greatly. Trypan blue injected into a lymph vessel of the foot of a dog may reach the receptaculum chyli in ten seconds, and sodium salicylate, injected similarly, can be detected in the lymph of the thoracic duct in one minute and twenty seconds. Bromphenol blue, injected intravenously, appears in the cervical lymph in two and a half minutes.

The flow of lymph is increased by increased functional activity of the part, by increased venous pressure and by general or local hyperthermia, but it is modified little, if any, by peripheral section of nerves and increased arterial pressure. Intravenous injections of solutions may cause increased flow of lymph by effecting a greater movement of water out of blood vessels or by injuring capillary endothelium, thus allowing proteinized fluid from blood to leak into the tissues. Inflammation causes an increased flow of lymph by increasing the blood flow, the venous, capillary and tissue pressure and the capillary permeability, unless the process is severe, when the flow of lymph may be decreased because of occlusion of the lymph vessels by pressure, thrombi, necrotic debris or fibrous tissue.

The pressure of cervical lymph in dogs is from 8 to 18 mm. of a solution of sodium carbonate, the specific gravity of which is 1.08, and in horses from 5 to 20 mm. of the same solution. The lymphatic pressure in the ear of a mouse is from 2 to 4 cm. of water. The pressure in the lymph vessel below the popliteal gland of the resting dog is undiscernible, but it increases to 68 cm. of water after forty minutes of passive exercise. Lymph vessels will stand a surprising amount of pressure without rupture and without serious incompetence of valves. Sterile inflammation may increase peripheral lymphatic pressure to 120 cm. of water.

Constituents of Peripheral Lymph—The protein in peripheral lymph of dogs varies from 1.84 Gm. per hundred cubic centimeters when at rest to 0.5 Gm. when active. Fibrinogen and prothrombin are present in lymph, but platelets are absent. Leukocytes, of which about 95 per cent are lymphocytes, vary in number from 403 to 68,000 per cubic millimeter. Occasionally, erythrocytes are found when the subject is at rest, and as many as 13,000 per cubic millimeter are present when the subject is active. The carbon dioxide-combining power of lymph is about 50 volumes per cent. The amounts of nonprotein nitrogen, urea, creatinine, sugar and chlorides in lymph are slightly greater than in blood plasma, but the amounts of amino-acids, total phosphorus and calcium are slightly less.

Coagulation of Lymph—As stated, lymph contains fibrinogen and prothrombin, but it clots more slowly (from ten to twenty minutes) than blood (from four to six minutes), owing to deficiency of thromboplastic

substance ordinarily supplied in a large degree by blood platelets that are absent in lymph. This deficiency is corrected and coagulation of lymph occurs whenever cells in contact with the lymph stream undergo necrosis, or whenever lymph stasis and living bacteria in lymph coexist.¹² When thrombosis of the lymph vessels occurs, the thrombi contract and shrink away from the wall of the vessel, leaving adequate space for the circulation of lymph, except when the coagulating process is progressive. Lymph vessels may be completely filled with thrombi in the region of a phlegmon.

Various foreign substances injected into an area of severe inflammation do not pass into the lymphatic capillaries, but the same substances, when injected intravenously, accumulate rapidly in the inflamed area. Both observations are explained on the basis of thrombosis of the lymph vessels and the presence of a fine network of fibrin which obstructs the flow of lymph away from the inflamed area.

EXPERIMENTAL STUDIES OF LYMPHEDEMA

Lymphedema can be produced by the removal of the lymph hearts in animals. Reichert¹¹ showed that complete excision of the iliac and inguinal lymph nodes of dogs and cats did not produce edema, even ligation of the iliac or femoral vein added to this procedure was not followed by edema. In further experiments, he divided the limb of a dog transversely, leaving in continuity only a carefully denuded femoral artery and vein, the edges of the wound were then carefully resutured. The resultant edema occurred on the second day, reached its maximum on the fourth or fifth day and subsided completely on the seventh or eighth day. After the eighth day, ligation of the femoral vein caused no recurrence of edema, but occlusion of the lymph vessels by injection of foreign particles caused its reappearance. When excessive scar tissue was produced in the incision in the skin and subcutaneous tissues, the edema remained for ten days or more, and injections of india ink revealed blockage of some of the superficial lymph vessels. These experiments indicate that lymphedema can be produced, but with considerable difficulty, owing, doubtless, to free collateral circulation at the root of the leg, a factor too little emphasized.

Hommans⁸ felt that the swelling of the limb in phlegmasia alba dolens could not be explained on the grounds of venous occlusion alone. Experimental ligation of veins of animals did not produce edema, and examination of swollen limbs in patients with phlegmasia alba dolens impressed him with the probability that lymphatic obstruction was an important factor in production of the edema. He ligated the common and internal iliac veins in dogs, injected 5 cc. of a broth culture of

¹² Opie, E. L. Thrombosis and Occlusion of Lymphatics, J. M. Research
29 131 (Nov.) 1913

Streptococcus viridans into the femoral vein and ligated it distal to the point of injection¹³ Characteristic phlegmasia alba dolens occurred India ink was injected into the paws of the edematous legs, and after a suitable time the animals were killed India ink was found at the level of the lower ligature, from this point to the inguinal ligament there was no pigment, but the common iliac nodes were loaded with particles of ink Homans concluded that the experimental procedure caused a periphlebitic reaction sufficiently extensive to block temporarily the perivascular lymph vessels of the trunk He pointed out how suitable the anatomic arrangements for such a condition are, all lymph vessels of the lower limb join at the groin to form trunks which hug the veins closely, and which may even be embedded in the adventitia of their walls¹⁴ All the vascular trunks, arterial, venous and lymphatic, are closely bound together in a tough, fibrous sheath From clinical and experimental observations, Homans felt that the cause of phlegmasia alba dolens is obstruction of lymph vessels, but that the basic lesion is always in the common or external iliac vein

Zimmerman and de Takats¹⁵ injected a solution of sodium salicylate or tincture of iodine into isolated segments of the common and external iliac veins of dogs, and in some instances sprinkled some of the solution along the outside of the vein In all animals there was a periphlebitic reaction, even to necrosis of perivenous tissues, but edema did not occur In further experiments, they dissected the iliac lymph nodes and all the retroperitoneal, fatty and areolar tissues from the bifurcation of the aorta to Poupart's ligament, and from the posterior parietal peritoneum to the psoas muscle They then ligated and divided the common and internal iliac veins There was no edema in eight animals, transient edema in two and marked edema in one

In another experiment, these investigators injected material into the femoral vein of dogs below the point of ligature Alcohol produced marked edema, but since objections might be raised to the use of it on the basis of the periphlebitic inflammation produced thereby, bland substances were used also Tissue extract, fibrinogen and barium sulphate in gelatin all produced marked edema when injected into the femoral vein below the point of ligature Injections of india ink into the footpads of animals with edematous legs indicated that the lymph vessels were permeable¹⁶

13 Homans, John, and Zollinger, Robert Experimental Thrombophlebitis and Lymphatic Obstruction of the Lower Limb, *Arch Surg* **18** 992 (April) 1929

14 Homans, John Thrombophlebitis of the Lower Extremities, *Ann Surg* **87** 641 (May) 1928

15 Zimmerman, L M, and de Takáts, Géza The Mechanism of Thrombophlebitic Edema, *Arch Surg* **23** 937 (Dec) 1931

16 Unless a specific reference has been given in the preceding paragraphs, authority is from the monograph of Drinker and Fields¹

CLASSIFICATION OF LYMPHEDEMA OF THE EXTREMITIES OF MAN

The cases of lymphedema studied lend themselves to division into two main groups, inflammatory and noninflammatory, the terms infectious and noninfectious could be used as well. The division into the two groups indicates the original state, lymphedema which is originally noninflammatory may be complicated eventually by inflammatory changes. Most cases of lymphedema may be classified without difficulty according to the tabulation.

Noninflammatory Lymphedema—Primary Lymphedema "Lymphedema praecox" is an original term applied to a definite clinical syndrome manifested in ninety-three cases in the group studied. It affected female patients predominantly (87 per cent of the cases), and in the majority of instances (65 per cent) had its onset between the ages of 10

Classification of 300 Cases of Lymphedema

	Cases
A Noninflammatory	
I Primary	
Praecox	93
Congenital	
1 Simple	12
2 Familial (Milroy's disease)	0
II Secondary	
Malignant occlusion	32
Surgical removal of lymph nodes	61
Pressure	1
Roentgen and radium therapy	3
B Inflammatory	
I Primary (single or recurrent acute and chronic)	41
II Secondary (single or recurrent acute and chronic)	
Venous stasis	13
Trichophytosis	5
Systemic diseases	5
Local tissue injury or inflammation	34

and 24 years, inclusively. The term "praecox" is used here to denote an early development, in many of the cases in this group the onset of symptoms occurred at puberty, and the incidence of onset in adolescence was impressive.

The swelling occurs spontaneously and without known cause, at the onset, the patient ordinarily notices a puffiness about the foot or ankle. The edema is worse during long periods of activity, during the menses and in warm weather. Rest in bed and elevation of the extremity produce temporary disappearance of the edema that may affect one lower extremity exclusively (70 per cent in this series) or both legs simultaneously, or one extremity may swell months or years after the opposite member has become involved.

The edema ordinarily progresses up the leg slowly, and eventually the entire limb becomes edematous over a period of months or years. The spread of the edema may, however, be much more rapid, the entire limb may be involved within a few days or weeks. In many instances,

swelling is limited to the foot and ankle or does not extend above the knee. Frequently, this particular state is doubtless merely a phase of a progressive condition, but in other instances it seems to represent the maximal degree of extension of the edema.

Gradually the swelling, whatever its limitations, becomes more marked, elevation and rest in bed cause its reduction but not its disappearance. The smooth skin becomes toughened, and the hitherto soft edema becomes resistant to pressure. In addition to enlargement of the limb due to edema, there is actual hypertrophy of tissue, and the limb becomes unsightly, ungainly and uncomfortable. A dull, heavy sensation is present, but there is no actual pain.



Fig 1—Lymphedema praecox in a woman, aged 39 years. Progressive edema of the right leg began at the age of 24 and gradually spread from the ankle to the inguinal ligament.

The entire course of the swelling is ordinarily one of smooth progression, acute lymphangitis and cellulitis occur infrequently (in 13 per cent of the cases studied). Ulceration of the skin does not occur. The entire history is ordinarily that of conversion of a normal limb into a swollen one, nothing else is noteworthy.

The cause of lymphedema praecox is obscure. The predominant incidence among female patients, the onset in the majority of cases during adolescence and the accentuation during menstruation tend to indicate that the reproductive organs play a part in the condition. Possibly the additional load thrown on the lymph vessels by rapidly developing repro-

ductive structures induces a functional incompetence of the lymph vessels or allows entrance of infection into the lymph trunks and nodes in the pelvis. Even minor degrees of functional inadequacy, through obstruction in the pelvis, might lead to dilatation of the lymph vessels below, with incompetence of the valves, particularly among women, whose subcutaneous tissues offer little support. The resulting interference with the free passage of tissue fluid into the lymph vessels provides adequate encouragement for the growth of fibroblasts and further obstruction by connective tissue. While such an explanation of the etiology is highly logical, it is equally theoretical. It is possible that the entire explanation rests on a congenital underdevelopment of lymph



Fig 2—Congenital lymphedema in a girl, aged 7 years. Parents noticed the left leg was larger than the right leg on the second day after birth. Enlargement has been progressive since then.

vessels, or their inability to develop quickly enough to supply adequately tissues that are growing rapidly. Limitation of the disease to the lower extremities is striking, and it indicates that gravity is an important factor in the development.

Congenital Lymphedema. This may be either simple or familial. In both types, lymphedematous swelling, usually of one lower extremity, is present at birth. There may be actual hypertrophy of the limb, true elephantiasis. In other instances, the skin is soft, and the edema is less resistant to pressure. The two forms do not vary, except that in the

simple type blood relatives are not similarly affected. In the familial type, several persons in the same family have lymphedematous swellings of one or more extremities. The familial type, known as Milroy's disease, was first described as a clinical entity by him in 1892. Milroy¹⁷ said

Briefly stated, chronic hereditary edema consists in a firm edema. It is limited in extent to the toes or a part or the whole of one or both feet, or of one or both

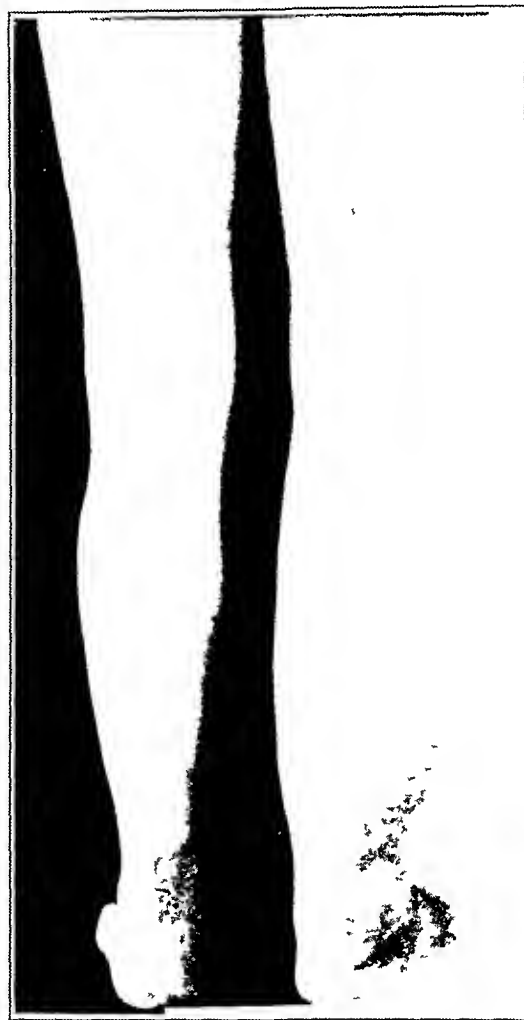


Fig 3—Secondary inflammatory lymphedema in a man, aged 60 years, who was kicked on the tibia by a mule fourteen years previously. The skin was not broken. Eight months later, a sequestrum was removed from the right tibia. No further trouble was experienced until seven years later, when the leg began to enlarge. The swelling was progressive. Roentgenologic examination at the time of admission gave evidence of old osteomyelitis of the tibia.

legs. It never extends above Poupart's ligament. It is not painful or tender and is without constitutional symptoms. It arises from no apparent cause. Hereditary transmission is conspicuous in its behaviour.

¹⁷ Milroy, W. F. Chronic Hereditary Edema. Milroy's Disease, *J. A. M. A.* 91:1172 (Oct 20) 1928.

Milroy's original report was based on a study of six generations of a family of ninety-seven persons, of whom twenty-two had lymphedema, twenty-one of the twenty-two having been born with the condition. Variations from the criteria of Milroy have been so great that the term "Milroy's disease," as used concurrently, is largely without significance. Meige¹⁸ found only eight cases in four generations, the onset at puberty was striking. Hope and French¹⁹ reported thirteen cases among forty-two persons in five generations, in no instance was the condition con-

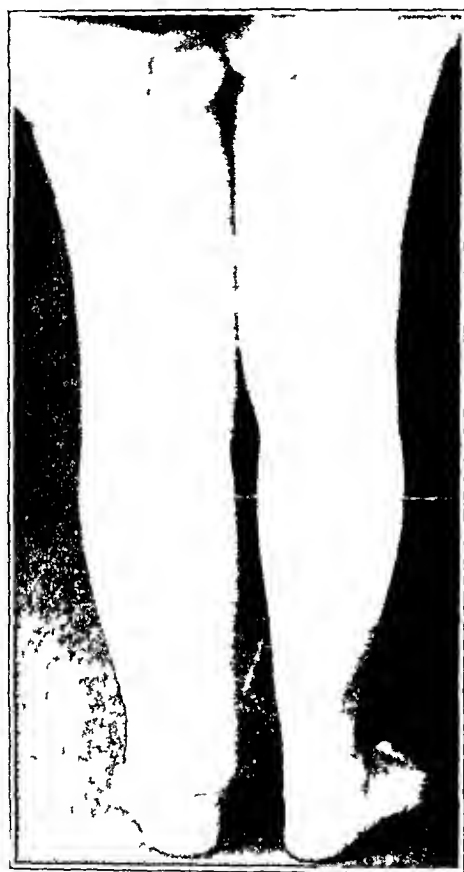


Fig 4—Secondary inflammatory lymphedema associated with trichophytosis in a woman, aged 55 years. A vesicular itching lesion of the skin of the toes, dorsum and plantar surfaces of the left foot had been present for four years. Attacks of acute lymphangitis and cellulitis recurred and edema had been present for three and one-half years. At the time of examination, trichophytes were found in the cutaneous lesions.

genital, the time of onset ranged from infancy to manhood, and attacks of recurrent cellulitis and lymphangitis occurred. There were no instances of Milroy's disease in this series of cases. Occasionally, a patient stated

¹⁸ Meige, Henry, quoted by Milroy.¹⁷

¹⁹ Hope, W. B., and French, Herbert. Persistent Hereditary Edema of the Legs with Acute Exacerbations. Milroy's Disease. *Quart J Med* 1: 312, 1907.

that he or she believed that a relative was similarly affected with swelling of the extremities, but the details were vague, and in no instance was it proved that the lymphedema was both congenital and familial

That the criteria of Milroy have been departed from is to be deprecated. Familial lymphedema is not Milroy's disease, according to Milroy's definition, unless the condition is congenital. Many of the cases called "Milroy's disease" are doubtless examples of lymphedema praecox with a familial predilection. The marked hereditary and congenital features present in Milroy's cases have not been equaled in cases reported by others, the situation recorded by Milroy may be unique. This constitutes further reason for close adherence to the diagnostic criteria given. Congenital lymphedema is produced largely by lymphangiectasis, a developmental anomaly.

Secondary Lymphedema. This may be due to malignant occlusion of lymph vessels by metastasis to adjacent lymph nodes of malignant disease of the breast, uterine cervix, uterus, vulva, prostate gland, bladder, testes, skin or bones. Such a possibility serves to emphasize the necessity of close scrutiny for evidence of malignant disease in all cases of lymphedema, since swelling may be the first outward manifestation. Pressure outside the lymphatic trunks perhaps occasionally, but rarely, produces lymphedema. The one case found in this series seemed to follow the use of a truss for inguinal hernia. Secondary, noninflammatory lymphedema may occur in cases of Hodgkin's disease or lymphosarcoma, or may follow surgical removal of lymph nodes and lymph vessels for malignant disease distally situated, or for tuberculosis or metastasis of malignant disease. The last named condition is the elephantiasis chirurgica of Halsted²⁰. Such a condition is not uncommonly seen following radical amputation of the breast and axillary lymph nodes for carcinoma. The lymphedema may occur with or without intervention of attacks of lymphangitis and cellulitis. The irregular interval at which lymphedema occurs after radical amputation of the breast is remarkable. Usually the arm begins to swell on resumption of activity, but weeks, months or even years may pass before the extremity becomes edematous. In one instance, the arm was free from swelling for nine and a half years, there was no evidence of the recurrence of malignancy to account for the edema, cellulitis and lymphangitis had not occurred. In such instances, it is possible that fibrosis may be induced by repeated irradiation, thus producing lymphatic obstruction, or that occult lymphedema over a period of years has resulted in overgrowth of connective tissue and obvious edema. Unfortunately, there are no experimental

20 Halsted, W. S. The Swelling of the Arm After Operations for Cancer of the Breast. Elephantiasis Chirurgica, Cause and Treatment, Bull. Johns Hopkins Hosp. **32** 309 (Oct.) 1921.

data to explain the occurrence of edema after radical removal of the breast, experiments on animals reveal that extensive removal of lymph nodes does not cause edema. Why, then, does this condition occur in man after extensive removal of lymph nodes? Halsted believed it was caused by infection following operation, either obvious or so slight as to avoid detection, or by recurrent attacks of cellulitis and lymphangitis. The question cannot be answered here. The answer may be inherent in the comparatively small number of experiments on animals, lymphedema has not been demonstrated in these experiments, but neither does it occur in many instances following radical removal of the breast in man. If larger numbers of animals were observed over greater periods of time following surgical removal of lymph nodes, it is probable that lymphedema would be noted. The conclusion based on clinical observation cannot be avoided, surgical removal of or metastasis to lymph nodes may produce lymphedema.

Lymphedema may occur after treatment with radium and roentgen rays. Whether such a result is brought about by the fibrosis caused by radiation, or by metastasis of the malignant disease for which radiation is given, cannot be determined with certainty. Barker²¹ described a case in which radium irradiation for a disease, apparently incorrectly diagnosed as carcinoma of the uterine cervix, was followed by lymphedema.

Inflammatory Lymphedema —General Characteristics. The advanced stage of inflammatory lymphedema has been called "elephantiasis nostras streptogenes." All examples of inflammatory lymphedema, exclusive of the chronic form, have one feature in common, single or recurrent attacks of acute cellulitis and lymphangitis. The contrast between lymphedema of inflammatory origin and of the praecox type is striking, in the former, progression is by a series of attacks which are impressive in the suddenness of onset, and striking in the severity of systemic reaction, in the latter, the history is one of slowly progressive edema. The usual victim of an attack of cellulitis and lymphangitis of an advanced grade is suddenly seized with a severe chill unpreceded by other symptoms, or, following a short period of distress in the extremity or proximal lymph nodes, his teeth chatter, the bed shakes and he becomes nauseated and vomits. His temperature is between 101 and 106 F, in a short time a small, reddened area spreads until a considerable portion of the extremity is swollen, red, hot and tender. The proximal lymph nodes are tender and swollen. The chills recur during a period of thirty minutes to an hour. The high fever persists for a period ranging from a few hours to two or three days, and is accompanied by marked malaise that may persist after the temperature returns to normal. The

21 Barker, N. W. Personal communication to the author.

abnormal condition of the extremity recedes slowly over a period of from four to fourteen days but, after all clinical signs of acute inflammation have disappeared, swelling is present in a greater degree than before the attack. The organism chiefly responsible for the attacks of acute inflammation is the streptococcus²

Single attacks leave minor degrees of lymphedema, but successive attacks, which tend to occur progressively, more frequently produce increasing edema, each attack is a step toward the final stage, namely, marked lymphedema and elephantiasis. The chronic form of lymphangitis of the spontaneous type is exceedingly rare. In such instances, the leg is persistently warmer than its companion member, and a reddish discoloration of the skin exists. In many instances, lymphedema following injury or infection develops without the intervention of acute attacks of lymphangitis and cellulitis or of clinical manifestations of chronic lymphangitis. The infection in such instances is considered to be sub-clinical. It should be emphasized that lymphangitis, whatever its nature, produces occlusion of lymph vessels by thrombosis or by the proliferation of connective tissue.

Primary Lymphedema. This term signifies a condition resulting from single or recurring acute attacks of chronic lymphangitis and cellulitis not secondary to any known local abnormality, such as venous or lymphatic stasis or extraneous infection. In many such instances, the lymphangitis appears to occur in much the same spontaneous manner as tonsillitis or phlebitis. In other instances, it may be due to infections introduced into the lymph vessels through minor portals of entry unnoticed by the patient. The acute attacks of lymphangitis and cellulitis have been described, each attack leaves a residue of increased edema. In the chronic form of lymphangitis, the edema is slowly progressive.

Secondary Lymphedema. This term indicates a condition resulting from lymphangitis secondary to known causes. The lymphangitis may occur in single or recurrent attacks or in a chronic form. Chronic edema of venous origin may predispose to recurrent attacks of acute cellulitis and lymphangitis, and thus to progressive lymphedema, but such instances are uncommon, in light of the rather common occurrence of thrombophlebitis resulting in edema.

Trichophytosis about the toes may induce recurrent attacks of acute lymphangitis. The inflammation and the resultant edema are ordinarily limited to the foot and ankle. It is probable that an etiologic relationship exists in but a small percentage of instances in which trichophytosis and acute attacks of lymphangitis occur in the same patient. It is not clear whether the trichophytes themselves or secondary bacterial invaders are responsible, even when the trichophytic infection seems to be definitely related to the acute inflammatory attacks. Instances which strongly sug-

gest that the trichophytes are directly or indirectly responsible for the acute attacks are those in which marked evidence of trichophytic infections, such as desquamation and the occurrence of vesicles, precede the appearance of cellulitis and lymphangitis. Pregnancy and systemic diseases such as influenza, typhoid fever, pneumonia, malaria and filariasis may lead to recurrent attacks of cellulitis and lymphangitis and result in lymphedema. Except in cases of filariasis, it is possible that the original lesion is thrombophlebitis that produces venous stasis, subsequent attacks of lymphangitis and, eventually, lymphedema. Occasionally, conversion into the lymphedematous state proceeds without the intervention of attacks of acute inflammation, in such instances, it is assumed that a condition of chronic lymphangitis exists, or that the lymph vessels become obstructed by overgrowth of connective tissue which is, in turn, a reaction to stasis of tissue fluid. Tissue fluid acts as an excellent culture medium, fibroblasts grow and fibrosis results unless the blood plasma is promptly returned to tubes lined with endothelium¹. It is worthy of note that filariasis was not demonstrated in any of the cases of lymphedema reported in this study. Clinical evidence of, or an antecedent history suggestive of, filariasis was consistently absent, in many instances, blood drawn from the patient at night was studied, but *Filaria* was never found. It is possible, if not probable, that filariasis existed in some of the cases reported, for it has been shown that failure to find *Filaria* does not exclude filariasis. The patients of the Mayo Clinic are drawn largely from northern climates where filariasis exists sporadically, if at all, and it is obvious that the absence of this condition as a cause of lymphedema would not hold in more southern locations where filariasis is common.

Local inflammation or injury of tissue leads to the production of lymphedema most commonly through the intermediation of single or recurrent attacks of lymphangitis or chronic lymphangitis. In the cases studied, such diverse causes as contusions, lacerations, surgical incisions, vesicles, abscesses, funicles, burns, fractures, penetrating wounds, dog-bites, tularemia abscesses, pelvic inflammatory diseases and appendicitis were directly responsible. The acute attacks may occur weeks or months after the original trauma, which may not be associated with any marked clinical evidence of infection. The organisms in the tissues appear to be in a "resting state," then, for some unknown reason, marked activity occurs, and an acute attack of cellulitis and lymphangitis is clinically apparent. It seems strange that minor abrasions should allow entrance of infection into the tissues, but Hadock and McMaster²² showed that

²² Hadock, S. S., and McMaster, P. D. The Lymphatic Participation in Human Cutaneous Phenomena. A Study of the Minute Lymphatics of the Living Skin, *J. Exper. Med.* **57** 751 (May) 1933.

the slightest wound of the corium may tear lymph vessels open and permit material to enter them directly. In many instances, the lymphedema occurred following injury or infection without the intervention of acute attacks of inflammation, and seemed to be due to a chronic or subclinical inflammation and thrombosis of lymph vessels or to a residue of inflammation from the original injury or infection.

DIFFERENTIAL DIAGNOSIS

There is rarely any difficulty in distinguishing advanced lymphedema, that is, elephantiasis, from edema due to other causes. The brawny indurated skin and the hypertrophied limb of elephantiasis bear little resemblance to manifestations of edema in other diseases. It is only when the lymphedema is not associated with changes in the appearance and feel of the skin that difficulty arises. Lymphedema can be distinguished without difficulty from the edema of general systemic diseases, such as myxedema, myocardial failure, nephrosis, nephritis or deficient proteinemia, when it is unilateral, when it is bilateral, a thorough examination is necessary to exclude these diseases. Sarcomas, lipomas and neoplasms of the bone are almost uniformly unilateral, and they produce regional or localized swellings, whereas the edema of lymphatic obstruction is more uniform and extensive. When swelling of an extremity is localized, careful roentgenologic studies are invaluable from a diagnostic standpoint. Angioneurotic and cyclic edemas are characterized by this intermittence, whereas lymphedema is more constant and disappears during the early phase only on elevation of the limb, well advanced lymphedema responds to this procedure incompletely. Enlargement of a limb in arteriovenous fistula is associated with dilatation of and increased pressure in the regional veins, analysis of the blood from these veins reveals an oxygen content approaching that of arterial blood. If the arteriovenous fistula is congenital, or was acquired before longitudinal growth of the bones ceased spontaneously, the limb is increased in length as well as in circumference. All these signs of arteriovenous fistula, except the increased circumference of the limb, are absent in lymphedema.

The edema of limbs occasionally noted in lymphosarcoma is probably of lymphatic origin, but recognition of the basic condition is important. Ordinarily, in cases of lymphosarcoma, there are enlarged nodes in the regions in which nodes are usually palpable, and in the mediastinum. Microscopic examination of a node removed surgically is invaluable when doubt exists. It may be remarked parenthetically that it is always important to examine patients with lymphedema carefully for evidence of malignancy. Lipodystrophy, characterized by "fat legs," is to be distinguished from lymphedema. Young women and girls with lipo-

dystrophy are subject to worry, anxiety and even to embarrassment at the supposed cosmetic disfiguration. Such reactions have arisen largely as a result of short dresses and hosiery advertisements, for aside from a slight disturbance in the symmetry of the body, no disfiguration exists. The condition, however, is as important as it appears to the patients. The characteristic symptoms which lymphedema and lipodystrophy may have in common are predilection for women, similarity in appearance, painlessness and additional swelling of the feet or ankles when patients are on their feet much, particularly in warm weather. Lipodystrophy is uniformly bilateral, and is usually associated with generalized obesity or obesity about the pelvis. The degree, but not the extent, of lipodystrophy may progress after it is first noted. In contrast, lymphedema is usually unilateral, is not ordinarily associated with obesity and usually progresses from the foot proximally, except when it is congenital. Attacks of lymphangitis and cellulitis may occur in lymphedema but not in lipodystrophy. Pitting on pressure may occur in both conditions, but it is less evident in lipodystrophy. The diminution in size, which may follow elevation of the extremities in both conditions, is more marked in lymphedema.

The edema of deep thrombophlebitis is usually to be distinguished from lymphedema because the former is similar to lymphedema in so many respects. Well advanced stages of either condition offer little difficulty in diagnosis. The hypertrophied limb, with the thickened skin and firm consistency, characteristic of elephantiasis, has little similarity to the limb in cases of deep thrombophlebitis, for the latter is marked by softer edema, stasis ulcers, dermatitis and superficial varices. To be sure, when attacks of recurrent lymphangitis or cellulitis occur, the leg that was originally edematous from venous obstruction acquires an additional element of lymphedema, and lymphedema may occur around varicose ulcers as a result of chronic infection. So far as I am aware, however, pure uncomplicated lymphedema, whatever its origin, does not lead to ulceration. It is in the earlier phases of the two diseases that difficulty is encountered, the usual similarity of symptoms includes unilaterality, pitting on pressure, normal skin texture and disappearance of edema following elevation of the limb. Dissimilarities exist in the circumstances of origin, speed of onset and progress, distress experienced by the patient and condition of the superficial veins. Thrombophlebitis with edema usually occurs in the course of or following an illness such as pneumonia or typhoid fever, or follows childbirth or operation. During the acute stage, a dull aching distress occurs in the area of the involved vein, which is tender to pressure, the edema develops rapidly to its fullest extent in the course of hours, and the superficial veins are dilated. Lymphedema does not ordinarily occur during systemic disease. The

absence of distress is striking, except when acute cellulitis and lymphangitis occur, the edema ordinarily develops to its fullest extent slowly over a period of weeks, months or years, and the superficial veins are not dilated. Among dissimilarities, the localized distress that occurs in thrombophlebitis is most important. Occasionally, the two conditions may coexist, as in the case of the thrombophlebitic limb that is involved in recurrent attacks of lymphangitis and cellulitis. In rare instances it may be difficult, if not impossible, to distinguish between the two conditions, although roentgenologic studies may be of some value.¹¹ The difficulty is particularly great when patients can relate only vague details about the development of the edema.

COMMENT

It is apparent that too little is known about lymphedema. In a study such as the one presented, much depends on the accuracy and details of the clinical history and examination of the patients. Invariably, when the study of patients with any specific condition has been carried out by diagnosticians having diverse interests, too much emphasis has been placed on diagnosis and too little on details of the history and the manifestations of the illness. My study suffers from this difficulty, which is offset somewhat by the fact that in recent years the study of lymphedema at the Mayo Clinic has been centralized. It is only by concentrated inquiry that minutiae of development can be traced in a consecutive manner, and it is only when this is done that facts about the evolution of lymphedema can be arranged in an orderly pattern.

The experimental data on lymphedema are, to say the least, confusing and somewhat contradictory, and at best are inadequate and almost inconsequential with respect to their worth in interpreting clinical phenomena. A condition simulating chronic lymphedema in man has not been produced in animals, and the experimental procedures so far executed appear insufficient when compared with those utilized in the production of venous edema.²³ Mechanical methods for interrupting the flow of lymph at the root of the leg should be, *a priori*, as devoid of results as those for mechanically interrupting the flow of venous blood. It is not surprising that resection of the pelvic and inguinal lymph vessels does not produce lymphedema, when it is considered that multiple ligations of veins in the same area do not produce venous edema. Experiments corollary to those producing venous thrombosis with venous

²³ Since this article was written a report of the experimental production of lymphedema by progressively occluding lymphatic vessels has been published (Drinker, C. K., Field, Madeleine E., and Homans, John. The Experimental Production of Lymphedema and Elephantiasis as a Result of Lymphatic Obstruction, *Am J Physiol* **108** 509 [June] 1934)

edema are necessary, namely, lymphatic thrombosis. Too little is known about the collateral circulation of lymph at the juncture of the extremity and the body. Although it is valuable to point out that all lymph vessels join at the groin and axilla and pass along the large blood vessels, it is important to know about the connection of lymph vessels below these regions with the lymph vessels of the abdominal and thoracic walls and of the back. Inasmuch as collateral circulation of the venous blood may be carried on by collateral channels from the root of the limb to the trunk, it is probable that an analogous situation exists for lymph vessels, at least, the analogy between veins and lymph vessels holds in every other important regard.

Even the clinical diagnosis of lymphedema is sometimes uncertain, a situation best illustrated by the equivocal parts played by lymphatic and venous obstruction in phlegmasia alba dolens. This situation is due to the absence of conclusive tests for lymphatic obstruction. Solution of the problem of distinguishing lymphedema from other types of edema may be found in analysis of the fluid in the edematous areas, in tests for speed of circulation of lymph in the extremities or in some method of visualization of the lymph vessels with dyes or by roentgen studies. I feel that the experimental production of chronic lymphedema would be an important step in the solution.

Finally, too little is known about the bacteriologic and pathologic changes in lymphedematous extremities. The etiology and the mechanism of production of lymphedema cannot be fully considered without the information gained from careful study of the pathologic changes and the bacteria involved.

I have pointed out some of the gaps in the knowledge of lymphedema in order to stress the need for further investigation, and to explain why it is impossible to present a completed picture of the disease. I feel that the shortcomings noted should encourage rather than discourage the investigator of lymphedema, the problems that remain unanswered are so important that any progress will be noteworthy.

SUMMARY

The important facts regarding lymph vessels and lymph are reviewed. A classification of lymphedema, based on a study of three hundred cases, is presented. Descriptions are given of the various types of lymphedema, and the mechanism of production is reviewed. Differential diagnosis of lymphatic edema and other types of edema is considered. The shortcomings in the knowledge of lymphedema are mentioned.

CARCINOMATOUS ENDARTERITIS OF THE PULMONARY VESSELS RESULTING IN FAILURE OF THE RIGHT VENTRICLE

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Hypertension of the pulmonary circulation with hypertrophy and consequent failure of the right ventricle is most frequently due to mitral stenosis or to chronic bronchitis and emphysema of long duration. The rôle of these mechanical causes of hypertension of the lesser circulation has been recently reemphasized by Moschcowitz¹. In a group of cases described by Eppinger and Wagner² and by others (MacCallum³) as primary sclerosis of the pulmonary vessels, the etiology of the vascular lesion is largely unknown. There is, however, a rather uncommon group in which diffuse metastatic carcinomatous lymphangitis is associated with widespread obliterative endarteritis of the pulmonary vessels. The widespread obliterative endarteritis causes a generalized narrowing of the pulmonary circulation followed by right ventricular hypertrophy and finally right ventricular cardiac failure.

In 1874, Troisier⁴ described an interesting clinical picture in patients with carcinomatous lymphangitis of the lungs secondary to carcinoma of the stomach. In describing his cases he commented on the paucity of the physical signs of disease in the lungs. He was concerned primarily with a description of the lymphatic spread of the process and made no mention of the presence of any vascular changes. In the same year, Raynaud⁵ and Hillairet⁶ published reports of similar cases. They also

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1 Moschcowitz, E. Hypertension of the Pulmonary Circulation, *Am J M Sc* **174**:388, 1927

2 Eppinger, H., and Wagner, R. Zur Pathologie der Lunge, *Wien Arch f inn Med* **1** 83, 1920

3 MacCallum, W. G. Obliterative Pulmonary Arteriosclerosis, *Bull Johns Hopkins Hosp* **49** 37, 1931

4 Troisier. Cancer de l'estomac, Cancer secondaire des poudons. Lymphangite pulmonaire généralisée, *Bull Soc anat de Paris* **48** 834, 1873, *Recherches sur la lymphangite pulmonaire*, Thèse de Paris, no 142, 1874

5 Raynaud, M. Lecture d'une memoire sur l'angioleucite généralisée des poudons, *Bull et mém Soc méd de hôp de Paris* **11** 66, 1874

6 Hillairet, M. Observations d'angioleucite pulmonaire dans le cancer de l'estomac, *Bull et mém Soc méd de hôp de Paris* **11** 78, 1874

stressed the involvement of the lymph vessels within the lung and pleura, but did not state whether the blood vessels revealed any pathologic changes. Girode, in 1889,⁷ was the first to mention the occurrence of endarteritis of the pulmonary arteries in lymphangitis carcinomatosa, but he considered the involvement of the lymphatics by carcinoma to be the important pathologic change.

Girode was aware of the fact that metastases to the lungs could occur by direct extension via the hepatic veins or vena cava system and give rise to pulmonary emboli. However, he believed that the most frequent route for pulmonary metastases was by way of the thoracic duct with a retrograde spread to the cervicomediastinal lymph nodes and to the pulmonary lymphatics, a view in which Bard⁸ later concurred.

The French authors were of the opinion that the clinical picture of dyspnea, cyanosis and cardiac failure was the direct result of the pulmonary lymphangitis carcinomatosa, and that vascular changes need not be present. They believed that the compression effects of carcinomatous lymphangitis on the bronchioles and alveoli were adequate to explain the clinical findings.

In 1897, Schmidt⁹ reported the finding of tumor cells from a carcinoma of the stomach in branches of the pulmonary arteries. He pointed out that narrowing and obliteration of the pulmonary arterioles were responsible for the hypertrophy of the right ventricle in his case. Later, in 1903, he published a monograph¹⁰ on the modes of metastasis of carcinoma. The occurrence of hypertrophy of the right ventricle was noted in one case of metastatic carcinoma of the lung. In this study, forty-one cases of carcinoma originating in abdominal viscera were examined, in twenty-eight of which there were metastases to the lungs. Of these, fifteen showed carcinoma cell emboli in the pulmonary arterioles without any macroscopic alterations in the parenchyma of the lung. The stomach was the site of the primary growth in seven of the fifteen cases.

Schmidt believed that these tumor emboli spread into the pulmonary vessels via the thoracic duct, the right subclavian vein, the superior vena cava and the right side of the heart, and thence into the pulmonary arterioles. According to him, many of the tumor cell emboli acquire a platelet deposit during their passage through the blood stream. After the emboli lodge in the arterioles, the thrombotic deposit increases by the

7 Girode, J. Lymphangite cancéreuse pluro-pulmonaire sans cancer du poumon, *Arch. gén. de méd.* **1** 50, 1889.

8 Bard, L. La lymphangite pulmonaire cancéreuse généralisée, *Semaine méd.* **26** 145, 1906.

9 Schmidt, M. B. Ueber Krebszellenembolien in den Lungenarterien, *Verhandl. d. deutsch. naturforsch.*, Braunschweig, 1897, no. 15, p. 11.

10 Schmidt, M. B. Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarcome zu den leukaemischen Neubildungen, Jena, G. Fischer, 1903.

further apposition of blood elements. Subsequently the tumor cells disintegrate, the thrombotic material becomes organized, and there results either total fibrous obliteration of the lumen of the vessel or the formation of a pillow-like projection into the lumen of the vessels. Schmidt pointed out that sometimes a secondary deposit of new thrombotic material or of new carcinoma cells occurs on an old fibrosed plaque, after which one may observe within the same arteriole vascular changes of different stages which are easily distinguishable from one another (fig 1)



Fig 1—Carcinomatous endarteritis of a small artery showing recanalization with recent thrombus formation

Except for the report by Baird⁸ in 1906, and an occasional mention of this condition in some of the German textbooks on pathology, no further mention of this condition was made until the publication by von Meyenburg¹¹ in 1919 and that of Ceelen¹² in 1920.

While the French writers deserve the credit for recognizing the gross pathologic changes in carcinomatous lymphangitis of the lungs and for

11 von Meyenburg, H. Zur Kenntnis der Lymphangitis carcinomatosa in Lungen und Pleura, *Cor-Bis für schweiz Aerzte* 49 1668, 1919

12 Ceelen, W. Ueber einem Fall von Thrombendarteritis pulmonis carcinomatosa, *Med Klin* 16 94, 1920

the observation that the tachypnea and cyanosis are out of proportion to the physical signs in the lungs, the striking histopathologic picture was first described by Schmidt twenty-three years after Troisier's report, and the clinical picture was described in detail by von Meyenburg and Ceelen. The characteristic syndrome is therefore well established in the French¹³ and German literature, but it has not been reported in the English or American publications. The following cases are therefore described in order to call attention to the condition.

REPORT OF CASES

CASE 1—L. K., a white woman, aged 40, was admitted to Mount Sinai Hospital (service of Dr. B. S. Oppenheimer) on Aug. 22, 1929. The family history was irrelevant.

A cholecystectomy and an appendectomy had been performed seven years previously, and an exploratory laparotomy for symptoms of peptic ulcer four years ago. Eleven weeks prior to admission a nonproductive cough developed which was accompanied by a dull pain in the chest and by frequent night-sweats. The cough became increasingly troublesome, and five weeks after its onset dyspnea, progressively increasing weakness and hoarseness developed. Four weeks later the patient was awakened from sleep by a choking sensation in the chest followed by a brief syncope. That night she had three similar attacks of suffocation. These episodes recurred frequently after that time.

One year prior to admission the patient discovered a small mass in the right breast which was painless to palpation. A similar painless mass was felt in the opposite breast. Both masses had enlarged rapidly during the last month. There was no history of hemoptysis, chills or fever.

Physical Examination—The patient was chronically ill, moderately emaciated and dyspneic and coughed frequently. There was a congenital bilateral internal strabismus. A small lymph node was palpated on the right side of the neck. In the outer quadrant of each breast, firm, hard, nodular masses which were not fixed to the skin or deeper structures were noted. Except for the presence of a moderate number of moist rales, there was a distinct paucity of physical signs in the lungs. The heart was not enlarged. There was a systolic murmur over the pulmonic area. Radial pulses were small in volume but equal. No masses were felt in the abdomen. Several small lymph nodes and one large one were found in the right axilla; in the left axilla there were several small nodes. The lymph nodes were freely movable and not stony hard.

Laboratory Examination—Studies of the blood revealed hemoglobin, 60 per cent, red cells, 5,000,000, white cells, 13,000, polymorphonuclear leukocytes, 78 per cent, lymphocytes, 16 per cent, monocytes, 4 per cent, and basophils, 2 per cent. The systolic blood pressure was 82 and the diastolic, 68. The Wassermann reaction of the blood was negative. On admission, chemical examination of the blood revealed 19 mg. of blood urea per hundred cubic centimeters.

Diagnosis—A diagnosis of chronic bilateral cystic mastitis was made, the possibility of a malignant change in the tumors of the breasts and of pulmonary metastases was considered.

13. A report in the *Presse médicale* (41:745 [May 10] 1933) by A. Costedoat entitled "La lymphangite cancéreuse des poumons" came to my attention after this paper had been prepared for publication.

Course—Throughout the patient's stay in the hospital, the temperature remained about 100 F. The dyspnea, which was strikingly apparent on admission, became increasingly conspicuous.

The first night in the hospital the patient was suddenly awakened from sleep by coughing. She felt faint but did not lose consciousness. She perspired profusely, and it was noted that the lips became deeply cyanotic. The pulse became imperceptible for about one minute, and then the rate increased to 104 per minute and remained irregular and weak. During this period the respirations were rapid and somewhat shallow, the rate, however, was not recorded. The "attack" lasted about ten minutes, after which the patient slept comfortably for the remainder of the night. The following day she had a similar attack, except that she lost consciousness for about one minute. These attacks recurred frequently. She was constantly troubled by the dry, raspy cough which had been present on admission.

Three days after admission, Dr. Harry Wessler reported that the roentgen picture of the chest was very suggestive of "lymphangitis carcinomatosa."

The persistent tachypnea (from 30 to 35 per minute) without orthopnea or cyanosis raised the question of acidosis as a possible cause of the rapid respiratory rate. However, the carbon dioxide-combining power of the blood was reported to be 39 volumes per cent. A biopsy, performed on a supraclavicular lymph node four days after admission, was reported by Dr. Paul Klemperer to show "metastasis of a signet ring cell carcinoma with excessive fibroplastic tendencies."

Electrocardiographic tracings one day before death were reported to show "right axis deviation, T₂ and T₃ showed cove-plane inversion."

Under observation, symptoms and signs of failure of the right side of the heart rapidly developed, cyanosis appeared, the liver gradually enlarged, a right hydrothorax and then a small amount of ascites developed.

Embryocardia appeared one day before death. The diagnosis of carcinomatosis of the heart was suggested before death to explain the picture of progressive myocardial failure from which the patient died six days after her entrance to the hospital.

Autopsy—The essential changes found at postmortem examination are summarized.

Macroscopic Examination Externally, there was marked cyanosis of the face, lips, ears and nail beds. Each breast contained a firm mass approximately 8 by 4 cm. These masses, which were in the upper and outer quadrant, were not adherent to the underlying skin and did not involve the nipple. Section of the masses in the breast revealed a firm, white, almost cartilaginous tissue that suggested carcinoma.

Both pleural cavities contained a small amount of clear straw-colored fluid. The lungs were free from adhesions. Except for distended, white, prominent lymphatic vessels, the pleurae were smooth and glistening. The lungs weighed 1,280 Gm. The pleural lymphatics were prominent, thickened and infiltrated by a white tissue which formed a cordlike tracery over the surface of the lungs. The lungs were subcrepitant. Numerous pinpoint to pinhead sized nodules were palpated throughout both lungs. On section, it appeared as if all the lymphatic channels were thickened and contained firm white tissue. The intervening lung was grayish brown. There were several anthracotic lymph nodes, which on section revealed an infiltration of firm, white tissue. The branches of the pulmonary arteries presented scattered areas of atheroma. The pulmonary veins presented no gross changes.

The heart weighed 400 Gm. The pericardium contained a slightly increased amount of straw-colored fluid. The pericardial surfaces were smooth and glisten-

ing throughout. The apex of the heart was composed of both ventricles. The right side of the heart was markedly enlarged, owing mainly to a hypertrophied and slightly dilated right ventricle. The valves and endocardium were grossly normal. The left auricle and ventricle showed no significant changes. The aorta presented occasional scattered atheromatous plaques. The coronary arteries were patent throughout and not narrowed.

The liver weighed 1,475 Gm. It was firm and reddish brown. On section, the normal architecture was greatly disturbed and completely replaced by irregular areas of yellow regenerating hepatic tissue interspersed with reddish portions forming a mosaic picture typical of a "nutmeg liver." The hepatic veins were markedly dilated, and the central veins deeply congested. The portal vein and biliary passages were grossly normal.

There was a large, flat, firm tumor located on the lesser curvature about 5 cm below the esophagus extending to within 4 cm of the pylorus. On section, this tumor was seen to be composed of a diffusely infiltrating, grayish-white tissue causing a marked thickening of the wall of the stomach and presenting several superficial small ulcerations. Lymph nodes along the curvature of the stomach were markedly enlarged and infiltrated by grayish-white tumor tissue.

Microscopic Examination. The histologic picture of the neoplasm of the stomach was characteristic of a scirrhous adenocarcinoma.

The pleura was thickened, owing to an increase in connective tissue, and contained a moderate sprinkling of lymphocytes, plasma cells and an occasional polymorphonuclear leukocyte. The pleural lymph spaces contained nests of tumor cells, some of which were of the "signet ring" variety. Frequent mitoses in the tumor cells were encountered. Occasionally single carcinoma cells were seen in the tissue spaces.

The connective tissue septums containing the large and small bronchi and vessels were greatly thickened. The septums were made up of richly vascularized connective tissue in which a dense infiltration of lymphocytes, plasma cells and polymorphonuclear leukocytes was seen.

The alveoli near the septums were frequently collapsed, while others were emphysematous. The alveoli contained a small amount of edema fluid, some desquamated alveolar epithelium and a few iron-containing macrophages.

The large arteries possessed a markedly hyperplastic intima which consisted of a thick layer of fibers in the subendothelial region, while the outer portions were formed by a loose interlacing network of connective tissue fibers containing a few fine elastic fibers. The media presented a mucoid change of the ground substance. The adventitia was trabeculated and thickened.

The small arteries of the 2 mm size frequently presented a narrowed or at times a completely obliterated lumen. The obliteration or the narrowing of the lumen, which was more often eccentric than concentric, was brought about by a loose connective tissue proliferation of the intima. Serial sections revealed that the lumens of these arteries were compromised to various degrees along the course of the artery, in places the narrowing was the result of a plaque-like lesion encroaching on the lumen of the vessel (fig 2). Frequently an obturating thrombus of fibrin, often containing a single or many carcinoma cells, was found in the lumen of a narrowed artery. The media of these vessels was greatly compressed. The adventitia was difficult to distinguish from the dense and increased perivascular connective tissue which was often edematous and was infiltrated by many plasma cells, lymphocytes and a few polymorphonuclear leukocytes. The perivascular lymph vessels contained large nests of tumor cells.

A growth of carcinoma cells into the outer walls of an artery, extending into the lumen, was not observed in this case. The veins showed no changes.

In summarizing this case, a scirrhous carcinoma of the stomach with pronounced metastases to the lymph channels is reported. Both lungs showed diffuse involvement of the lymph vessels by carcinoma. Marked proliferation of the intrapulmonary connective tissue septum with an inflammatory reaction was present. The arterioles, especially the smallest, showed a severe intimal proliferation which in many instances resulted in a complete obliteration of the lumen. The obliteration was at times caused by plugs of fibrin which frequently contained carcinoma cells.

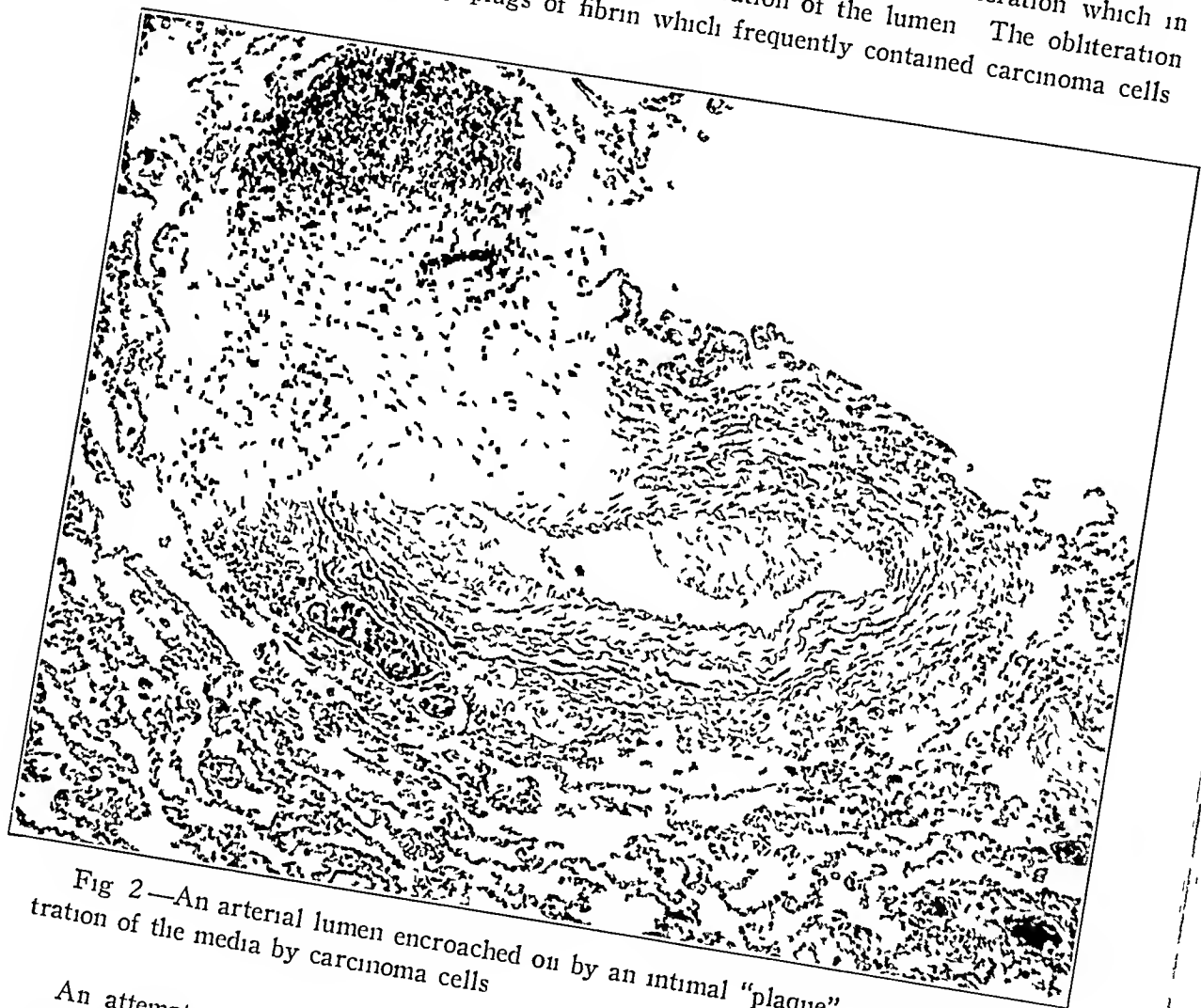


Fig 2—An arterial lumen encroached on by an intimal "plaque", note the infiltration of the media by carcinoma cells

An attempt to establish conclusively the etiology of the intimal proliferation from the histologic picture is difficult. However, one might assume that the same fibroplastic factor that is responsible for the extensive increase in the perivascular connective tissue might also be responsible for the intimal hyperplasia. In any event, there was no evidence present to indicate an obliteration of the lumen by carcinoma cell proliferation. The single carcinoma cell emboli which were embedded in the plugs of fibrin also cannot satisfactorily explain the diffuse spread of obliterative endarteritis.

The tumor masses in the breasts revealed a histologic picture similar to that seen in the primary tumor of the stomach.

Anatomic Diagnosis—The diagnosis was infiltrating scirrhus carcinoma of the stomach (limitis plastica) with metastases to both breasts, skin, ovaries, lungs and tracheobronchial lymph nodes, lymphangitis carcinomatosa of the lungs and obliterative endarteritis of smaller arteries and the arterioles, hypertrophy and dilatation of the right ventricle, chronic passive congestion of the liver, fibromyomas of the uterus, and cystic endocervicitis

Summary—A white woman, aged 40, presented a history of a dry, nonproductive cough, frequent night-sweats and later dyspnea and weakness

Examination revealed masses in both breasts, small intracutaneous nodules over the middle of the clavicle and a moderate number of moist râles in the chest

The clinical course was characterized by rapidly increasing tachypnea and cyanosis terminating in failure of the right ventricle

The electrocardiographic tracings indicated a right ventricular hypertrophy, the roentgen picture of the chest was suggestive of lymphangitis carcinomatosa

At autopsy, a scirrhus carcinoma of the stomach was found with lymphangitis carcinomatosa of the lungs and an obliterative endarteritis of the pulmonary vessels

CASE 2—J L, a man, aged 38, was admitted to the Mount Sinai Hospital (service of Dr Leo Kessel) on April 12, 1932 The past history was unimportant

The patient stated that he was well until one year before About that time occasional attacks of localized pain developed in the lower portion of the abdomen which subsequently shifted to the left lower quadrant, with radiation to the epigastrium The pain was mild and occurred from one to two hours after eating, being relieved somewhat by food and alkalis, but mainly by vomiting After roentgen examination of the gastro-intestinal tract, the patient was informed by his physician that he had a stenosing peptic ulcer and was placed on a bland diet and advised to use alkalis With dietary precautions he was symptom-free for about seven months, until three weeks before his admission to the hospital A feeling of fulness in the upper portion of the abdomen and vomiting after meals developed, and the patient complained of marked anorexia His symptoms became progressively worse, a week later he began to cough and expectorated about an ounce of mucopurulent sputum daily Shortly after the onset of the cough, he became dyspneic At first his dyspnea was mild, but it gradually became so severe that at the time of admission to the hospital it was his most prominent symptom, even while at rest There had been a loss of 25 pounds (11.3 Kg) in weight in the last eight months

Physical Examination—The patient was robust, slightly obese and dyspneic There was a distinct pallor of the skin and mucous membranes, but no cyanosis or edema The veins in the neck were not distended The chest was barrel-shaped No dilated veins were noted over the wall of the chest There was diminution of pulmonary resonance below the angles of the scapulas where the breath sounds were increased in expiration, and occasional crackling râles could be heard The bases of both lungs moved freely The heart was not enlarged, the sounds were of good quality, rhythm was regular and no murmurs were heard The aortic second sound was louder than the pulmonic second sound The abdomen was markedly distended, particularly in the epigastric region where direct and rebound tenderness was noted The liver was palpated three and a half finger-breadths below the right subcostal margin There was no peripheral edema or clubbing of the fingers or toes

Laboratory Examination—Studies of the blood revealed a hemoglobin of 69 per cent, 9,000 white cells per cubic millimeter, 82 per cent polymorphonuclear leukocytes, and 14 per cent lymphocytes The blood pressure was 94 systolic and 70

diastolic The Wassermann reaction of the blood was negative Chemical examination of the blood revealed 18 mg of urea per hundred cubic centimeters, 515 mg of chlorides and a carbon dioxide-combining power of the plasma of 48 volumes per cent Examination of the urine gave negative results The guaiac test for occult blood in the stool was negative The Rehfuess test meal revealed a total acidity of 44 with a free acidity of 25 only after the administration of 0.5 mg of histamine, subcutaneously Gastric aspiration yielded 20 cc of yellow nonbloody fluid The electrocardiographic tracings showed a tendency to right ventricular preponderance with the R and T waves low in all leads

Diagnosis—A diagnosis of peptic ulcer with pyloric stenosis was made, carcinoma of the stomach was to be excluded

Course—In the ward, the patient's temperature fluctuated between 100 and 102 F, with a pulse rate of about 86 and a respiratory rate between 20 and 24 per minute Roentgenologically, the pulmonary fields were clear, there was marked elevation of the diaphragm on both sides with a resultant upward displacement of the heart A series of roentgenograms of the gastro-intestinal region was reported as showing no abnormalities

Four days after admission, signs of congestion appeared at the base of both lungs with presacral edema and ascites Dyspnea became more marked and was soon accompanied by orthopnea and deepening cyanosis, which was greatly exaggerated by effort The liver grew larger, and generalized edema became apparent With these and the electrocardiographic evidence of right ventricular preponderance, it was felt that progressive failure of the right side of the heart due to a myocardial lesion was responsible for the clinical picture, although the exact nature of the cardiac lesion was not known Another suggestion offered for the circulatory failure was that the failure was due to some mechanical obstruction to the great veins obstructing the return of the venous blood to the heart

Eight days after admission, the patient became psychotic and extremely cyanotic and died in circulatory collapse

Autopsy—The body was that of a well nourished man in incomplete rigor mortis There was slight pretibial edema The peritoneal cavity contained about 1,500 cc of straw-colored fluid

Each pleural cavity contained approximately 300 cc of straw-colored fluid The visceral pleurae of both lungs presented numerous yellowish-white distended lymphatic vessels On the diaphragmatic surface of the lower lobe of the right lung and in the middle lobe were several small, firm, dark blue areas The lungs were moderately voluminous and generally crepitant except for a small area occupying the upper lobe of the right lung On section, the lungs were red and congested and presented a faint brownish tint The upper lobe of the right lung was fleshy, and much frothy fluid exuded from the lower lobe The small, firm, dark blue areas were wedge-shaped and represented infarcts Throughout both lungs, but most marked in the lower lobes, were numerous grayish-white, pinpoint to pinhead sized nodules which caused the lungs to feel finely nodular The smaller septums stood out as prominent gray strands The pulmonary arteries showed an occasional atheromatous plaque In the middle lobe an adherent reddish thrombus occluded the lumen of a medium-sized vein The bronchial mucosa was reddened Both lungs presented the same gross anatomic picture

The pericardial sac contained about 200 cc of straw-colored, clear fluid The heart was flabby and small The right ventricle was moderately dilated and distinctly hypertrophied The left ventricle was not hypertrophied The valves and endocardium were normal

The liver was moderately enlarged and firm and presented a smooth capsule with rounded edges. On section, a variegated appearance was seen, such as is seen in the "nutmeg" liver of chronic passive congestion.

An indurated, flat, smooth, grayish-white plaque with scalloped edges measuring 6 cm in diameter was seen on the lesser curvature of the stomach about 5 cm from the pyloric ring. On sectioning the plaque, firm, homogeneous, grayish-white carcinomatous tissue about 5 mm thick was found. The gastro-hepatic ligament for a distance of about 10 cm was indurated and diffusely infiltrated. The regional lymph nodes did not appear to be grossly involved.

Microscopic Examination The histologic picture of the tumor of the stomach was typical of a scirrhus adenocarcinoma.

The lymph vessels surrounding the large and smaller arterial branches frequently contained masses of tumor cells. The perivascular connective tissue was distinctly increased. It consisted of thickened nuclear-poor connective tissue which was infiltrated in the periphery by many lymphocytes and few polymorphonuclear leukocytes. The adventitia merged into the perivascular connective tissue mantle from which it could not be differentiated. The media of some of the smaller arteries was definitely narrowed, but showed no other changes. Many of the smaller arteries showed a marked intimal proliferation which narrowed the lumen of many of the vessels and caused a complete obliteration in others. The intimal proliferation was not always circumferential but was mostly localized and resulted in plaque-like lesions. The elastic interna of these vessels was distinct and not lamellated. The thickened intima consisted of nuclear-poor connective fibers which were interspersed with frequent fine elastic fibers. Occasionally, the narrowed lumen of one of the vessels was further occluded by a plug of fibrin. Tumor cells were not present in the lumen of the vessel in this case.

In resumé, this is a case of a scirrhus carcinoma of the stomach with metastases to the regional lymph nodes and infiltration into the gastro-hepatic ligament and pancreas.

There was marked plugging of the perivascular lymphatics of the lung with carcinoma cells and marked perivascular fibrosis with an inflammatory cellular infiltration. The intima of many arteries showed a definite thickening, often resulting in complete obliteration of the lumen. Plugs of fibrin were present within the lumen of the vessel although no tumor cell emboli were found.

In this case the fibroplastic stimulation resulting in the marked intimal proliferation, often leading to complete obliteration, might also be ascribed to the presence of the carcinoma cells in the perivascular lymph channels, as carcinoma cell emboli are not seen here.

Anatomic Diagnosis—The diagnosis was scirrhus adenocarcinoma of the stomach with metastasis to the regional and peripancreatic lymph nodes, gastro-hepatic ligament and pancreas, lymphangitis carcinomatosa of both lungs with thrombo-endarteritis of the smaller pulmonary arteries and the arterioles, hypertrophy and dilatation (moderate) of the right ventricle, chronic passive congestion of the liver ("nutmeg"), spleen and kidneys, anasarca (ascites, hydrothorax, hydropericardium, edema of the lower extremities and sacrum), acute pulmonary edema, pulmonary infarcts of the middle and lower lobes of the right lung, and thrombosis of the pulmonary vein of the middle lobe.

Summary—A white man, aged 38, presented a one year history of epigastric pain, occurring from one to two hours after eating, loss of weight and a three week history of anorexia and vomiting after meals, followed two weeks later by cough and dyspnea.

Examination revealed a dyspneic, anemic-looking man. Pulmonary resonance was diminished below the scapular angles, where an occasional crackling râle could be heard.

In this case, the progressive right ventricular failure greatly overshadowed the gastro-intestinal symptoms. The roentgen examinations both of the gastro-intestinal tract and of the chest gave negative results. The electrocardiographic tracings indicated a tendency to right ventricular preponderance.

At autopsy, a scirrhous adenocarcinoma of the stomach was present, with metastases to the lungs in the form of widespread lymphangitis carcinomatosa of the lungs with a diffuse obliterating endarteritis of the small arteries and the arterioles.

CASE 3—O. H., a white man, aged 40, was admitted to the medical service of Dr. George Baehr on April 14, 1931. For the past ten years he had experienced vague epigastric discomfort, mild anorexia, headache and occasional vomiting. Two and one-half months before admission he became markedly constipated and occasionally complained of severe pain in the upper abdominal region which usually appeared from fifteen to thirty minutes after eating. Weakness and loss of weight followed the onset of the intestinal disturbance. Two months later a nonproductive cough developed. About this time asthenia became so marked that he had to go to bed. His weight had decreased from 130 to 105 pounds (59 to 47.6 Kg.) in the past two and one-half months.

Examination revealed a chronically ill, wasted man. There were a few crepitant râles at the bases of both lungs. The heart was not enlarged, there were no murmurs. The pulmonic second sound was accentuated, split and louder than the aortic second sound. The abdomen was generally distended. A questionable mass descending with respiration was palpated in the left hypochondrium. No clubbing of the fingers or toes and no edema or cyanosis were found.

Laboratory Examination—Studies of the blood revealed a hemoglobin content of 78 per cent with 7,600 white cells. The differential count revealed 81 per cent polymorphonuclear leukocytes, 11 per cent lymphocytes, 5 per cent monocytes and 3 per cent eosinophilic leukocytes. The blood pressure was 128 systolic and 72 diastolic. The Rehfuess test meal showed the absence of free hydrochloric acid in the gastric content, each specimen aspirated was grossly bloody. The stool was reported to contain occult blood. The urinary findings were not significant. Sigmoidoscopic examination gave negative results. Roentgen examination of the colon with an enema of barium sulphate showed only a marked depression of the midportion of the transverse colon with some constriction in this region which was interpreted as "suggestive of adhesions." Roentgen examination of the chest showed a diffuse mottling of both lungs which was considered to be due either to an artefact resulting from the roentgen technic or to developing tuberculosis. The Wassermann reaction of the blood was negative.

Diagnosis—A diagnosis of an intra-abdominal malignant condition was made.

Course—Except for increasing restlessness, the patient's course was uneventful until four days after admission, when he suddenly went into collapse without cyanosis. His pulse suddenly rose to 150 per minute, with a respiratory rate of 54 per minute. The temperature was 101.4 F. The patient complained of marked weakness, faintness, dizziness and thirst. The blood pressure reading was 80 systolic and 70 diastolic. Examination revealed that the mucous membranes were pale and the skin cold and moist. The pulmonary fields were clear, and except for tachycardia examination of the heart gave essentially negative results. The hemoglobin was unchanged. Two hours later the patient "appeared very restless,

apprehensive, almost gasping for breath" At this time physical examination gave the same results as it had earlier in the evening Rectal examination revealed no blood or tarry stool on the examiner's glove As the hemoglobin was still 78 per cent, hemorrhage was considered unlikely The patient died one hour later, four days after admission

Autopsy—The essential changes found at postmortem examination are summarized The lungs presented a similar appearance The pleurae were studded with numerous tiny white nodules In places there were whitish-gray branching streaks outlining the lymphatic vessels On section, the lungs were congested and everywhere studded with sharply defined, tiny white nodules the size of a millet-seed In places the lymphatics appeared like tiny twigs The tracheal and bronchial lymph nodes were considerably enlarged, and on section revealed tumor tissue

The heart was not enlarged The valves, endocardium and myocardium presented no gross abnormalities The coronary arteries were normal

There was a moderate amount of free fluid in the abdominal cavity The omentum was rolled up and firm and contained numerous white, firm tumor nodules There was a deposit of neoplastic tissue partly lining the culdesac A firm nodular mass in the wall of the stomach was densely adherent to the peritoneal structures

The liver was moderately enlarged and congested

The capsule of the spleen was covered with numerous small metastatic nodules The hilus was densely adherent to the stomach and the head of the pancreas and was encased in a neoplastic mass

The pancreas was completely surrounded by neoplastic tissue which infiltrated the substance in some areas The splenic and mesenteric vessels were not compressed or infiltrated

Along the entire lesser curvature of the stomach a flat, ulcerated, neoplastic mass was found This tumor infiltrated the entire posterior wall of the stomach, producing a diffuse thickening and presenting the appearance of linitis plastica All the regional lymph nodes extending to the porta hepatis, the peripancreatic nodes and the periaortic nodes, which encased the aorta without compressing it, were enlarged by metastases The inferior vena cava was not involved, and the thoracic duct was lost in the neoplastic tissue, but no tumor tissue was seen within it, grossly, the lumen appeared intact

Microscopic Examination—The gastric neoplasm was a scirrhous adenocarcinoma of the stomach, presenting the picture of linitis plastica

Throughout the lungs the perivascular connective tissue septums were thickened The perivascular lymph vessels were distended with masses of tumor cells At times single tumor cells could be seen within the tissue spaces Frequent mitoses were present The connective tissue surrounding the blood vessels showed marked infiltration of polymorphonuclear leukocytes and lymphocytes Frequently an arterial wall was found to be penetrated by tumor cells and presented a polymorphonuclear leukocytic infiltration The lumen of the great majority of the small arteries and the arterioles contained adherent masses of tumor cells showing frequent mitoses Frequently the tumor cells were enmeshed in a fibrin plug which partially or completely closed the lumen Occasionally, early organization of one of these plugs was seen Often the lumen of these vessels was narrowed or completely obliterated by a connective tissue proliferation of the intima which was infiltrated by polymorphonuclear leukocytes and single tumor cells

In this case a scirrhous adenocarcinoma of the stomach with extensive metastases to the lymph nodes, liver and peritoneum was present The lungs showed a

widespread filling of the septums, lymph channels and spaces by tumor cells and a connective tissue proliferation with a diffuse inflammatory reaction. The walls of the small arteries and the arterioles were frequently infiltrated by tumor cells which often plugged the lumens of these vessels and presented numerous mitoses. Some of the lumens were closed by tumor-fibrin thrombi, while others presented an obliterating intimal proliferation infiltrated by polymorphonuclear leukocytes and tumor cells. In this case the genesis of the obliterating endarteritis might be ascribed to infiltration around and into the vessel causing a marked fibroplastic stimulus and not, as Schmidt believed, to multiple carcinomatous emboli. It is still questionable whether the carcinoma masses in the lumen of the vessel could not be explained by an autochthonic proliferation of tumor cells which had penetrated into the lumen.

The veins did not show any significant changes.

Anatomic Diagnosis—The diagnosis was scirrhus adenocarcinoma of the stomach with metastases to the regional and tracheobronchial lymph nodes, lungs, pancreas, liver and capsule of the spleen, lymphangitis carcinomatosa of the lungs and obliterating endarteritis of the smaller pulmonary arteries and arterioles.

Summary—A white man, aged 40, presented a two and a half month history of increasing constipation and occasional spontaneous pain in the upper abdominal region followed by weakness and loss of weight. Two weeks before admission a nonproductive cough developed. Examination revealed a chronically ill, wasted man. The thoracic findings were unimportant. Except for the terminal event of faintness, apprehensiveness and marked dyspnea, the symptoms were generally referable to the gastro-intestinal tract. At necropsy, a scirrhus adenocarcinoma of the stomach with pulmonary metastases was found. Besides the presence of lymphangitis carcinomatosa, an active thrombo-endarteritic process was strikingly conspicuous throughout the parenchyma of the lung.

CASE 4—H. W., a white man, aged 37, was admitted to the surgical service of Dr. Edwin Beer on July 16, 1931. The past history was unimportant except for an operation for perirectal abscess seven years previously. The patient stated that he had been in a good state of health until four months prior to his admission. About this time he became markedly constipated, and anorexia developed. Several days before his entrance to the hospital, severe diffuse pain developed in the upper abdominal region accompanied by several attacks of vomiting. Concomitant with the onset of the constipation he noted that he was short of breath after slight exertion and subsequently even while at rest.

Physical Examination—The patient was an emaciated dyspneic man who appeared quite ill. Respirations were rapid (30 per minute) and "grunty." The pulse rate was 144, and the temperature 103 F. There were coarse loud râles and squeaks heard over both sides of the chest. The heart rate was rapid, no enlargement or murmurs were noted. The lower portion of the abdomen was distended, tense and tender from the umbilicus down to the symphysis pubis. No masses were palpated. Digital rectal examination revealed a hard, almost stony mass which encircled the rectum, slightly narrowing the lumen, just at the tip of the examining finger.

Laboratory Examination—Examination of the blood showed a hemoglobin of 80 per cent, 6,000 white blood cells with 77 per cent polymorphonuclear leukocytes and 23 per cent lymphocytes. The urine contained albumin (2 +) and an occasional leukocyte. The stools were not examined. Because of the striking symptom of dyspnea, a roentgen examination of the chest was made soon after admission and

was reported by Dr Harry Wessler as suggesting "lymphangitis carcinomatosa involving both lungs in their entirety"

Diagnosis—The diagnosis was carcinoma of the rectum with peritoneal and pulmonary metastases and peritonitis secondary to perforation of a carcinomatous lesion

Course—While in the ward the patient's temperature varied between 103 and 104 F with corresponding increase in the pulse rate varying between 100 and 136. The respiratory rate averaged about 31 per minute. The patient vomited frequently and complained of epigastric pain. There was diffuse abdominal tenderness. Dyspnea became more marked, and six days after admission he suddenly experienced cardiac collapse, the pulse became very rapid and thready, breathing was labored, accompanied by a marked diaphoresis. Death occurred one hour later on July 22, six days after admission to the hospital.

Autopsy—Both pleural cavities were free from adhesions and did not contain any excess fluid. The lungs were well aerated and retained their shape. The visceral pleura presented numerous circular, umbilicated, firm nodules about 1 cm in diameter scattered over the surface of the lung. Some of these nodules were confluent and were arranged in clover-leaf fashion. The appearance of white, firm cords of tissue in the lymphatics, spreading out from these nodules, was striking. On section, many similar grayish-white nodules were seen scattered diffusely throughout the substance of the lung, appearing to occupy particularly the septums and the peribronchial and perivascular areas. The nodules were larger and more confluent near the hilus, decreasing in frequency toward the periphery of the lung. The nodular involvement was greatest in the lower lobes. The hilus and paratracheal nodes were greatly enlarged and on section presented a grayish-white homogeneous structure. The lungs weighed 1,850 Gm. The pulmonary vessels were grossly normal.

The heart weighed 280 Gm. There was no hypertrophy of the right ventricle. The valves, endocardium and myocardium were grossly normal.

The liver weighed 1,675 Gm. The surface was smooth, and the capsule was not thickened. It was firm in consistency and reddish brown. The edges were rounded. On section, the lobular structure was distinct, the centers of the lobules being reddish brown. There were two grayish-white, round tumor nodules in the hepatic substances, measuring 3 mm in diameter. The gallbladder, biliary passages and portal vein were normal. The lymph nodes in the porta hepatis were slightly enlarged.

The esophagus and stomach were essentially normal. The intestines were distended, being free in the upper part of the abdomen but densely matted in the lower half at the site of a peritoneal abscess formed after the rupture of a carcinoma of the sigmoid. The serosa, mesentery, mesocolon, mesosigmoid, omentum and parietal peritoneum all showed distinct, whitish-gray, firm, metastatic nodules, varying from 1 to 5 mm in size. A distinctive feature was that the nodules were arranged in a linear or lacework manner as if they corresponded to the local lymphatic channels. At the junction between the descending colon and the sigmoid, the intestinal wall was thickened and infiltrated by firm, white tissue which continued for a distance of 15 cm, the sigmoid finally narrowing to a diameter of about 1 cm, causing marked stenosis of the lumen. The mucosal surface in this area was a dark dirty gray but not ulcerated. Just proximal to the stenotic lumen, a fistulous tract communicated with a peritoneal abscess which contained foul pus, sharply walled off by loops of small intestine and omentum. The remainder of

the sigmoidal and rectal mucosa was not involved. In the pelvic cavity the bladder, intestines and peritoneum were densely infiltrated with tumor tissue.

There were marked metastases with enlargement of many of the lymph nodes in the abdominal and thoracic regions. The thoracic duct could not be identified because of permission for a limited postmortem examination.

Microscopic Examination—The tumor in the sigmoid was described as an adenocarcinoma of the "signet ring" variety.

All the metastases examined histologically revealed the type of tissue seen in the primary neoplasm of the sigmoid.

This case showed strikingly a pure lymphangitic carcinomatosis. The most marked histopathologic changes were found in the perivascular and peribronchial lymphatics which were greatly dilated owing to the pressure of huge nests of tumor cells composed mostly of the signet ring type. Many of these collections of cells showed abundant secretion. Occasionally a mitotic figure was seen. The tumor caused a distinct narrowing and distortion of both the bronchi and bronchioles and the medium-sized and small arteries. The alveoli were similarly compressed, and the capillaries of their septums were congested. It is noteworthy that no appreciable amount of intimal hyperplasia was encountered.

Anatomic Diagnosis—The diagnosis was adenocarcinoma of the sigmoid (signet ring cell type), lymphatic carcinomatosis of the peritoneum, mesentery, mesosigmoid, retro-aortic and retromediastinal nodes, bladder and intestines, lymphangitis carcinomatosa of the lungs, subacute infectious splenic swelling, metastatic nodules in the liver (minimal), and carcinomatous infiltration of the left ureter with left hydronephrosis.

Summary—A 37 year old white man presented a history of constipation, anorexia and progressively increasing dyspnea for four months. Several days before entrance to the hospital severe pain in the upper abdominal region developed. Examination revealed an emaciated dyspneic man. The respiratory rate was 34 per minute. There were definite coarse râles in both sides of the chest. A stony hard mass was felt in the rectal wall. The presence of tachypnea with coarse râles in both sides of the chest in a case of neoplasm of the sigmoid led to the suspicion of pulmonary metastases—a suspicion which was confirmed by roentgen examination of the chest and autopsy.

At necropsy, an adenocarcinoma of the rectum was found with widespread lymphangitic metastases to the lungs without any histologic evidence of intravascular changes in the pulmonary vessels.

COMMENT

Pathology—Of the four cases of carcinomatous lymphangitis of the lungs, only one (case 4) conforms with the picture of pure lymphatic dissemination stressed by the French authors. In this case the mediastinal lymph nodes were greatly enlarged by metastases from a carcinoma of the sigmoid. There was a diffuse involvement of the lymphatic vessels of the lungs which greatly compressed not only the alveoli but also the bronchioles, the medium-sized and smaller arteries and the arterioles. No endarteritic changes were noted in any of the vessels in this case.

In three of the four cases the presence of tumor cells in the perivascular lymphatics had called forth a marked increase in adventitial connective tissue as well as an intimal hyperplasia in many of the smaller

arteries and arterioles Varying degrees of arterial obliteration were produced, often with complete closure of the lumen This was especially conspicuous as widespread lesions in cases 1 and 2, and less widespread lesions in case 3

It is perhaps more than a coincidence that the primary neoplasm in these three cases with vascular changes was a scirrhous carcinoma of the stomach In some of the smaller arteries the intimal response might be ascribed to the invasion of the adventitia and a partial destruction of the media by scirrhous carcinoma In other arterioles and small arteries, even after serial sections had been made, no such invasion was found It is suggested that the presence of the carcinoma cells in the surrounding tissue exerted some stimulus which resulted in intimal hyperplasia and narrowing or occlusion of the vessels This was suggested by the observation of a more or less marked inflammatory reaction around and in the outer wall of the vessels

In routine microscopic examination of lungs showing lymphatic metastases from carcinomas of other abdominal organs, we have noted focal endarteritic changes in several instances, the affected vessels being surrounded by lymphatic vessels containing carcinoma cells

An additional cause for the narrowing of the pulmonary arterial bed was seen in the apposition of a platelet thrombus on the hyperplastic intima This thrombo-endarteritic process eventually resulted in either partial or total obliteration of the vessel Often an eccentric lumen or one or more recanalizations were encountered (fig 1)

Occasionally an embolus of carcinoma cells was found within a small artery or an arteriole in which varying degrees of obliterative endarteritis was present (fig 3) This phenomenon was most marked in case 3 However, in all three cases the obliterating endarteritis was mainly the result of the perivascular carcinomatous lymphangitis and not, as M B Schmidt believed, principally the result of multiple carcinomatous emboli within the pulmonary arteries

In sharp contrast to the fate of the carcinoma emboli in the arterioles and smaller arteries surrounded by lymphatic carcinosis is the end-result of carcinomatous emboli within the larger pulmonary arteries In the larger pulmonary arteries a carcinoma embolus undergoes organization without inducing appreciable intimal damage and eventually becomes covered by endothelium Such a sequence of events was recently observed in a case in which a primary carcinoma of the liver grew into the hepatic veins and resulted in the discharge of carcinoma cell emboli into the larger and medium-sized arteries Microscopically, the deposition of the carcinoma emboli seemed to have caused no intimal damage in the vessels containing the emboli The surface of the embolus (fig 4) was lined by endothelium

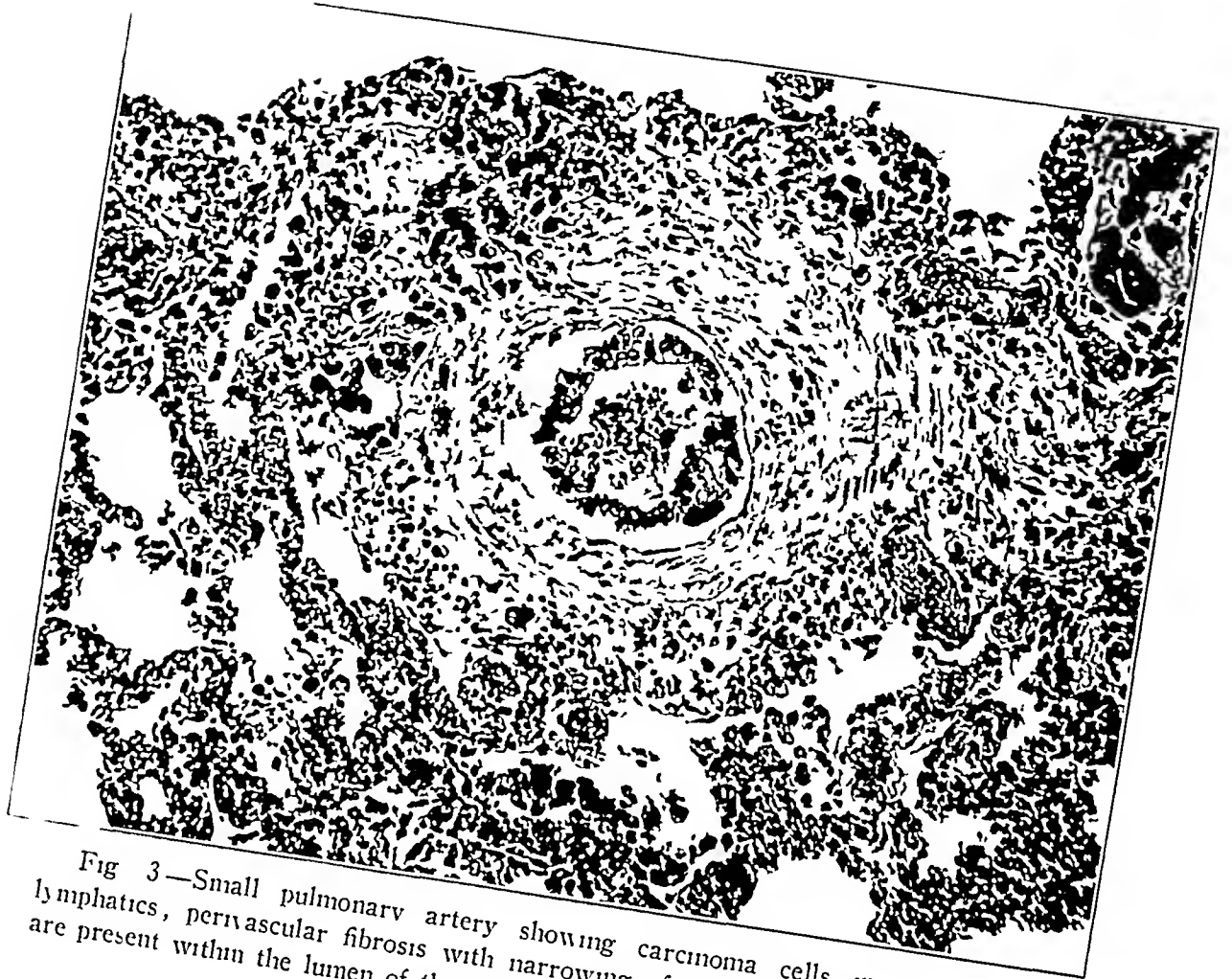


Fig 3—Small pulmonary artery showing carcinoma cells in perivascular lymphatics, perivascular fibrosis with narrowing of the lumen. Carcinoma cells are present within the lumen of the vessel.

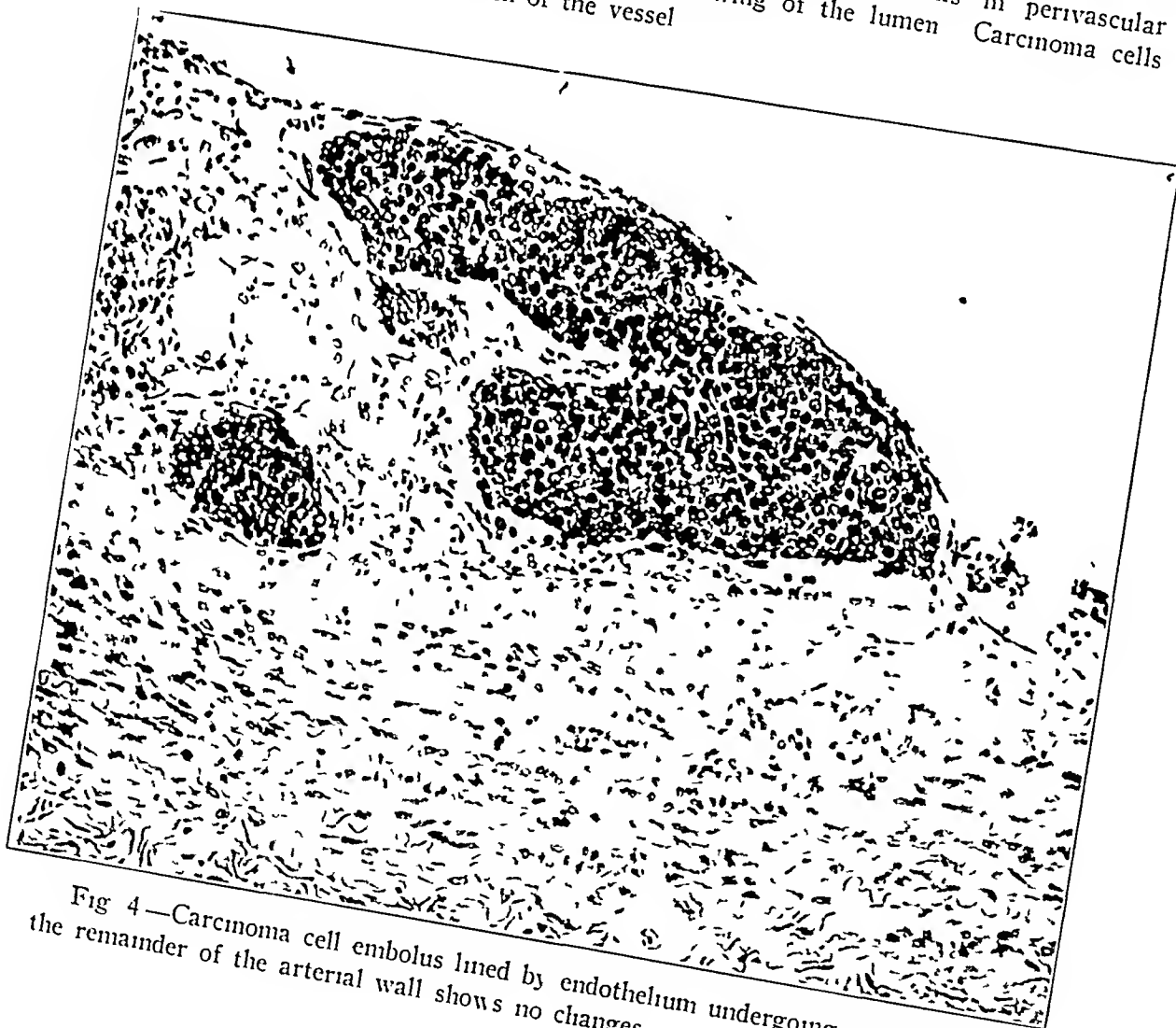


Fig 4—Carcinoma cell embolus lined by endothelium undergoing organization, the remainder of the arterial wall shows no changes.

and presented the usual changes characteristic of an ordinary pulmonary embolus undergoing organization. Another case serves to emphasize the difference between the end-results of emboli in larger arteries and in arterioles. In this case focal carcinoma cell emboli in the pulmonary arteries resulted from involvement of the hepatic veins by a carcinoma of the gallbladder. The intima of the large arteries which contained emboli showed no change although the perivascular lymphatics of the vessels contained tumor cells. In arterioles which contained carcinoma emboli and which were surrounded by lymphatic metastases, a typical obliterative endarteritis was regularly present.

Clinical Characteristics—Cases 1 and 2 presented a striking picture of progressive dyspnea, cyanosis and finally right ventricular cardiac failure. In the second case the increasing tachypnea, the deepening cyanosis with progressive enlargement of the liver and the generalized edema in the absence of diagnostic pulmonary or cardiac findings made the diagnosis difficult.

Case 3 revealed no clinical features indicative of the underlying pulmonary disease. In this case the increasing constipation with progressive loss of weight and weakness dominated the clinical picture.

In case 4 the presence of tachypnea with disparagingly few pulmonary signs and the presence of a carcinoma of the sigmoid prompted the diagnosis of carcinomatous lymphangitis secondary to a colonic neoplasm. In this case dyspnea was probably the direct result of the mechanical compression which not only diminished the available alveolar respiratory area but also narrowed the pulmonary circulation, thereby embarrassing the oxygen supply of the patient.

It is diagnostically important to bear in mind that when a clinical picture is presented of right ventricular failure without obvious cause and without any conspicuously abnormal physical signs in the lungs, the suspicion of carcinomatous lymphangitis of the lungs should be entertained, a fact that was pointed out by Troisier. Since neoplasms of any of the abdominal organs may give rise to pulmonary metastases, it is reasonable to expect that they may cause right ventricular failure. Excluding primary carcinoma of the bronchus, which usually gives conspicuous signs and symptoms in the respiratory tract, carcinoma of the stomach is (in our experience) the most frequent cause of carcinomatous lymphangitis of the lungs and arteriolar occlusions.

Dyspnea and cyanosis are the two most constant clinical features of failure of the right ventricle, and in the first two cases failure of the right side of the heart is clearly the result of the progressive obliteration of the pulmonary arterioles and the smaller arteries. Dunn¹⁴ has pro-

14 Dunn, J. S. The Effects of Multiple Embolism of Pulmonary Arterioles, *Quart J Med* **13** 129 (Jan) 1920.

duced multiple embolisms of the pulmonary arterioles experimentally by intravenous injection of granules of starch. He found that with a degree of embolism insufficient to produce death there was a great increase in the frequency and a diminution in the depth of respiration (rapid shallow breathing).

The interpretation of the clinical findings is greatly aided by roentgen examination of the lungs. In cases 1 and 4 the presence of numerous streaks radiating from an enlarged hilar shadow made the pulmonary fields appear mottled and suggested the diagnosis of carcinomatous lymphangitis. Assmann¹⁵ and Wessler¹⁶ must be credited with having pointed out that this roentgenologic picture is suggestive of pulmonary carcinomatous lymphangitis.

SUMMARY

Four cases of carcinomatous lymphangitis are described.¹⁷ Three were secondary to scirrhous adenocarcinoma of the stomach and one to adenocarcinoma of the sigmoid. In all four, the physical signs of the pulmonary involvement were inconspicuous and yet the clinical picture was characterized by an initial cough and by rapidly increasing dyspnea and deepening cyanosis. Two of the four patients died with evidences of rapidly progressive failure of the right side of the heart. The roentgen diagnosis of carcinomatous lymphangitis of the lungs was confirmed by necropsy in two cases. In the three cases of scirrhous adenocarcinoma of the stomach, autopsy revealed a widespread obliterative endarteritis of the smaller pulmonary vessels. In two of these cases the vascular changes were sufficiently extensive to explain the failure of the right side of the heart.

This obliterative endarteritis is due mainly to the influence of the plugging of the neighboring perivascular lymphatic channels by carcinoma, so-called carcinomatous lymphangitis. The vascular occlusions result to a minor degree from carcinoma cell emboli which have entered the pulmonary circulation via the thoracic duct and the superior vena cava. A few carcinoma cell emboli were found which had accumulated blood platelet thrombi in their passage through the blood stream and subsequently had undergone rapid organization after they had come to lodge in small branches of the pulmonary arteries.

15 Assmann, H. *Klinische Roentgendiagnostik der inneren Erkrankungen*, ed. 3, Leipzig, F. C. W. Vogel, 1924, p. 314.

16 Wessler, H. Personal communication.

17 Since this presentation was made before the Pathological Society in May 1933 two other similar cases have been observed, one was observed through the courtesy of Dr. W. Antopol, pathologist to the Bayonne Hospital, Bayonne, N. J.

CONCLUSIONS

1 Four cases of carcinomatous lymphangitis of the lung are reported, three secondary to scirrhus carcinoma of the stomach and one secondary to an adenocarcinoma of the sigmoid

2 The four cases presented all or part of the pulmonary symptoms of cough, tachypnea and cyanosis with inconspicuous physical signs in the lungs

3 The three cases secondary to scirrhus carcinoma of the stomach presented diffuse obliterative endarteritis of many pulmonary arterioles and small arteries

4 The widespread obliterative endarteritis of the lung was due chiefly to the influence of the carcinomatous lymphangitis of the neighboring perivascular lymphatics, rarely to carcinoma cell emboli

5 In two of the cases right ventricular cardiac failure was the direct result of the diffuse obliterative endarteritis of the pulmonary vessels

6 In cases of right ventricular cardiac failure presenting no significant pulmonary or cardiac findings, the possibility of a diffuse secondary carcinomatous lymphangitis of the lungs with accompanying obliterative endarteritis of the pulmonary vessels should be considered

ACUTE ESSENTIAL HYPERTENSION PRECIPITATED BY MEDIASTINAL ABSCESS

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AND

ROBERT B RADL, M D

MINNEAPOLIS

While mediastinal abscess following trauma probably occurs infrequently enough to justify an individual report, the case under consideration challenges particular attention because of an associated acute arterial hypertension. Not only did hypertension of pronounced intensity of both systolic and diastolic phases develop directly and coincidentally with the process, but there was a gradual fall to normal limits as healing occurred. No similar instance was found in a rather extensive search through the medical literature. The implications as to the theory of the etiology of essential or nonrenal hypertension stimulate the imagination, although admittedly an acceptable rationalization may elude us at this time.

REPORT OF A CASE

History—A man, single, aged 21, a student and a member of the football squad, was admitted to the University Hospital on Friday, Sept 23, 1932, with a complaint of pain in the chest, a chilly sensation and fever. The pain followed an injury sustained in football practice two days previously. The patient did not know or remember the incident of the injury, simply that at some time in the afternoon while in scrimmage his chest had been hurt. There had been no extreme pain, and he had indulged in three or four other scrimmages before being admitted to the hospital. The patient had been feverish since the injury, with chilly sensations during the second night.

His past history and that of his family were unimportant. A complete routine physical examination before the present illness revealed a displaced nasal septum due to a football injury, slight dental caries, tonsillar tags, varicocele on the left side and hemorrhoids. Urinalysis showed no albumin or sugar. The reaction to the Mantoux test was negative. The blood pressure five days before injury was 124 systolic and 86 mm of mercury diastolic. Examination one year previously had shown a blood pressure of 128 systolic and 84 mm of mercury diastolic.

Examination—On entrance, the temperature was 103 F, the pulse rate, 104, and the respiratory rate, 28. The pharynx was injected. There was tenderness over the entire sternum. No abnormal physical signs in the chest were noted, the breathing, however, was restricted bilaterally. Roentgenograms showed

From the Students' Health Service and the Department of Surgery, University of Minnesota

a linear fracture of the sternum without displacement 3 cm below the manubriosternal juncture. The lungs were normal.

Course—On the fourth day of continued high temperature, increased cough and sputum were noted. On the sixth day, slight cyanosis, an increased respiratory rate, fever and blood-tinged sputum, together with dullness and suppression of breath sounds and increased tactile fremitus above the right base posteriorly indicated pneumonia. There was moderate edema above the sternum. A roentgenogram showed infiltration above the right side of the diaphragm suggestive of a bronchopneumonia. The leukocyte count had increased from 8,000 to 13,500. *Pneumococcus* type A was recovered from the sputum. On the seventh day, increased swelling over the sternum was noted. On the ninth day, the temperature was lower and the general condition was satisfactory. On the tenth day, however, the patient appeared to be more prostrated and was extremely ill with

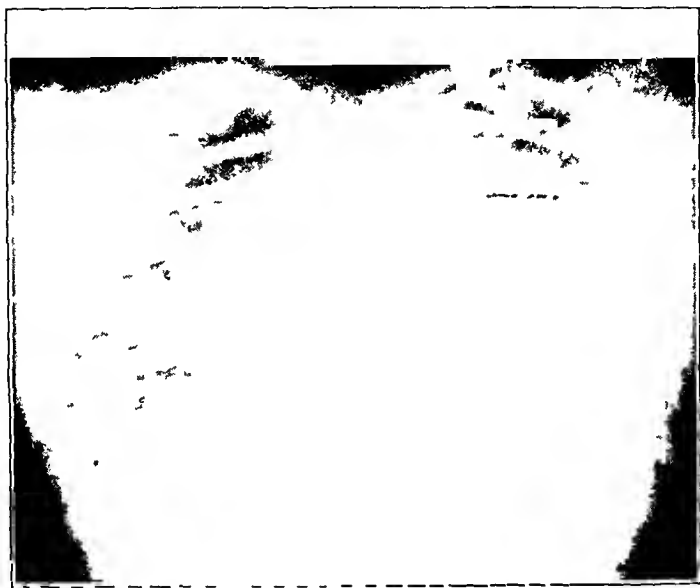


Fig 1—Roentgenogram of chest on tenth day of illness. This shows especially the widening of the mediastinum.

marked edema of the entire upper part of the anterior chest wall. The posterior part of the left pulmonary field showed impairment of resonance and diminished breath sounds. The heart tones were somewhat diminished. A pleuropericardial friction rub was heard along the left cardiac border, but no to and fro friction was noted. It was recognized that bronchopneumonia alone could not account for the clinical picture. Emphasis was placed on the significance of the edema of the sternum and upper part of the anterior thoracic wall, and mediastinitis was recorded as a probable diagnostic consideration. A roentgenogram taken on the tenth day of the illness (fig 1) revealed a decided change, interpreted as probably bronchopneumonia with possible fluid on the left side and marked widening of the mediastinum. The leukocyte count had increased to 21,800. A second blood culture was reported negative. On the eleventh day, there was continued marked prostration with increased cyanosis. Continued emphasis was placed on the edema of the upper part of the anterior thoracic wall which was considered to be of intrathoracic origin. The point of maximum cardiac impulse was forceful and

was noted 4 cm beyond the nipple line. No pericardial or pleural friction rub was heard. The systolic blood pressure was 142 mm, the diastolic pressure was not recorded.

On the twelfth day, the patient was more prostrated, the pulse rate had increased to 120, but the temperature was reduced to 99.8 F. This remarkable spread in the temperature and pulse (fig. 2) was coincidental with a decided increase in the systolic blood pressure to 194, indicating that a definite change in the control of the vasomotor function had occurred. The respiratory rate remained elevated between 36 and 40 when the patient was in an oxygen tent.

A remarkable physical finding which had appeared overnight, noted by one of us (C. A. McK.), was the presence of a fluctuating mass about 5 cm in diameter situated above and to the left of the midsternum. This mass definitely varied in size with respiration, increasing with expiration and decreasing with inspiration, showing its intrathoracic origin. The cardiac impulse was transmitted through the mass, although there was no expansile pulsation. The edema of the surrounding tissues had not increased.

A roentgenogram taken immediately after the discovery of the fluctuating mass was interpreted as showing extensive pneumonia or pleural effusion on the right side, resolving pneumonia on the left side and distinct narrowing of the mediastinal shadow as compared to the examination two days previously. This film does not lend itself satisfactorily for purposes of publication.

It now seems probable that the narrowing of the mediastinal shadow was due to the rupture of the mediastinal abscess into the anterior part of the thoracic wall and also into the right pleural cavity. The latter event is only conjecture, although injection of an opaque medium later showed a connection between the mediastinum and an anterior empyema pocket.

A diagnosis of abscess of the anterior mediastinum pointing through the sternum was made, with which Dr. S. Marx White and Dr. T. J. Kinsella, as consultants, concurred. Within five hours after its appearance and recognition, the abscess was drained through a left upper parasternal incision by one of us (T. J. K.), and 400 cc of thin purulent material was obtained. The pus escaped from the mediastinum through the fractured sternum, the edges of which were separated about 5 mm, and through a defect produced by the traumatic separation of the left third costal cartilage from the sternum. No accessory pockets were found in the mediastinum, but a left subpectoral pocket was opened and drained. Culture from the pus revealed both streptococci and staphylococci. An airtight dressing sealed with strips of adhesive tape was applied to prevent respiratory embarrassment from the sucking mediastinal wound. This was later replaced by a metal cage moulded to the contour of the thoracic wall and sealed to the skin, in which a constant negative pressure of from 10 to 15 cm of water was maintained by means of a suction pump. A removable cap permitted change of dressing without disturbing the skin seal.

A blood culture taken the day following drainage was positive for staphylococci. The leukocyte count had increased to 30,000. Roentgenograms showed a homogeneous density on the right and numerous areas of density on the left, and suggested an extensive pneumonia. On the second day following drainage, or the fourteenth day of the illness, the blood culture showed staphylococci on both broth and plate, and the wound smear and sputum showed a pure culture of the same organisms. Blood cultures on the fifteenth and sixteenth days showed fewer colonies, not more than six on a plate, and on the seventeenth and eighteenth days, no growth. On the twentieth day, the leukocyte count had fallen to 21,800, and on the twenty-seventh day, to 9,850.

Following development and drainage of the abscess, the temperature remained lower, but the pulse rate was accelerated, and the rate of respiration increased. Dyspnea was pronounced. Cyanosis was moderate, and the patient's comfort was enhanced by the oxygen tent. The blood pressure remained elevated. On the fifteenth day, another wave of increased temperature occurred. On the sixteenth day, however, the pulse rate was slower and there was definite improvement in the patient's general condition, with less labored breathing. There were no petechiae noted in the skin. On the seventeenth day, a small vesicular rash appeared at points of irritation on the skin, described as miliaria by a dermatologist, the leukocyte count reached 37,000. MacNeal bacteriophage (asparagine medium) was given intravenously at the suggestion of Dr. Diehl, director of the Students' Health Service, after his careful study of its specificity for the organism involved. Bacteriophage (veal broth mediums prepared by Dr. W. P. Larson) was dropped into the mediastinal wound four times daily. On the nineteenth day, general improvement was noted. Because of suggested signs of fluid at the base of the right lung, aspiration was attempted on the twentieth day, but no fluid was found. The temperature assumed a lower level (maximum, below 100 F), and the general condition remained satisfactory. On the twenty-first day, a roentgenogram showed considerable clearing of the shadows on both the right and the left side. By the twenty-seventh day a roentgenogram showed evidence of pleural effusion on the right side, although there was no change in the patient's general condition. On October 18, thoracentesis was performed and 60 cc. of thin pus was obtained posteriorly from the right pleural cavity. The temperature at this time varied from normal to 99.6 F, and the pulse rate from 90 to 100. There were no chills. Roentgenograms after injection of an iodopain derivative into the mediastinal wound showed a connection between this area and an anterior empyema pocket which may have allowed drainage of the empyema and accounted for its relatively benign character.

Aspiration of the empyema cavity was performed at intervals of from three or four days, and asparagine medium bacteriophage was injected at the times of aspiration. Streptococci and staphylococci were cultured in the empyema fluid. On November 1, a closed catheter drainage was done under ethylene anesthesia. At this time, the mediastinal wound was practically closed, although light drainage was still present. Crepitus was still present at the site of the fracture and a roentgenogram of the site of the fracture showed considerable destruction with, however, some new bone formation.

The empyema cavity was irrigated with a surgical solution of chlorinated soda thereafter at two hour intervals. The general condition was good, the temperature was 99.6 F, the pulse rate, from 100 to 110, and the respiratory rate, 24. On Dec. 5, 1932, the patient was discharged from the hospital with the drainage tube in place. Irrigation with solution of chlorinated soda was continued. On Feb. 11, 1933, the tube was removed after repeated cultures of the serous material obtained had shown no growth and the cavity held less than one ounce of it. The mediastinal wound was entirely healed. The blood pressure on numerous occasions was never more than 126 mm. systolic. Figure 2 shows a composite record for the first part of the illness.

The empyema cavity refilled, however, and after several aspirations a subperiosteal resection of portions of the eighth and ninth ribs on the right side was done March 15, 1933, under local infiltration with 1 per cent procaine and epinephrine, and ethylene anesthesia. The blood pressure, which at the onset of the operation was 130 systolic and 70 diastolic, rose ten minutes later to 200 systolic and 90 diastolic, and fluctuated from 160 systolic and 80 diastolic to 170 systolic

and 60 diastolic at the close of the operation. The subsequent course was quite satisfactory. Irrigation with the solution of chlorinated soda was continued, and the cavity gradually decreased in size, as shown by injections of iodized oil, until it was entirely obliterated. The tube was removed Sept 1, 1933. The mediastinal wound was likewise well healed, and a roentgenogram of the fracture showed firm union, with good callus. There had been considerable loss of weight, and muscular atrophy was quite evident, especially on the right side of the chest. With the resumption of the patient's normal activities, including football and basketball, there was return to normal of both body weight and muscular development.

The eyegrounds were considered normal on several examinations. The blood pressure in the lower extremities approximated that in the upper. Pressure over the sinus caroticus caused no appreciable alteration in the pulse rate.

Special attention was paid to renal function on account of hypertension, but at no time was there any evidence of nephritis. The urine was free from albumin.

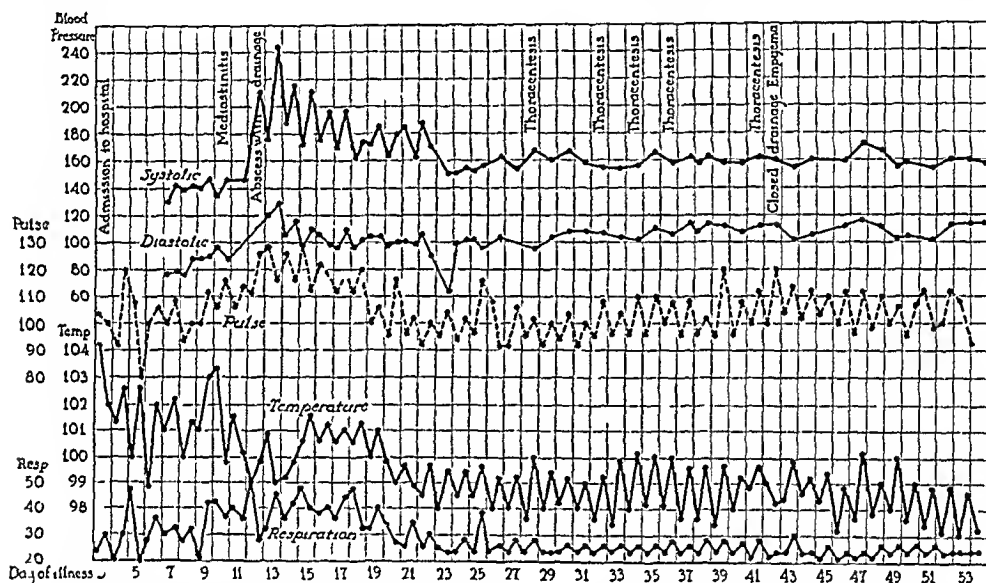


Fig 2—Composite chart of temperature, pulse rate, respiratory rate and blood pressure. Blood pressure had returned to normal on the seventy-fifth day of illness.

on seven of eight examinations, and at the time of the one exception, which occurred at the height of the fever and the pneumonic process, it contained only a light cloud. The specific gravity ranged from 1.017 to 1.030, and the sediment was entirely free from red blood cells and casts. The phenolsulphonphthalein test on the twenty-seventh day showed elimination of 68 per cent in two hours. The blood urea nitrogen on the thirteenth day, at the height of the pneumonic process, was 50 mg, but four days later it was checked at 28.9.

The possibility that this case might represent a potential case of hypertension or a prehypertensive stage was considered. In accordance with the recent work of Hines and Brown,¹ the vasomotor reaction after immersion of the hand in ice-water was obtained. Readings well within the normal response were found.

1 Hines, E. A., Jr., and Brown, G. E. Standard Test for Measuring Variability of Blood Pressure, Its Significance as Index of Prehypertensive State, *Ann Int Med* 7:209 (Aug) 1933.

The familial aspect of hypertension was investigated. The father and mother were each in good health. The blood pressure of the father (aged 53) was 160 systolic and 100 diastolic, the mother (aged 46) gave readings of 134 systolic and 80 diastolic.

COMMENT

Mediastinal abscess itself is rare. While it is not within the scope of this article to attempt a complete survey of reports of its occurrence, it may be mentioned that as long ago as Galen's time, mediastinal abscess was recognized, and this author recorded a case following trauma. Hare² collected a series of 115 cases of mediastinal abscess. Dunham³ noted in the army records of 3,889 nontraumatic cases of empyema, 67 instances of acute mediastinal infection in 531 necropsies. It may be noted that simple nonsuppurative mediastinitis is usually a complication of some nearby inflammatory disease, such as pericarditis, pleurisy or pneumonia. Gaarde⁴ called attention to the frequency with which suppurative mediastinitis or empyema was found post mortem in pneumonia complicating the influenza epidemic of 1918 and 1919. The chief diagnostic sign that he noted was substernal pain. He noted also that abscess was much less likely to give pressure symptoms than a solid tumor. Other causes noted by him were (1) trauma, especially puncture wounds, perforation of the esophagus due to ulceration caused by a malignant condition, corrosive poisoning or instrumentation and descending infections of the neck, such as Ludwig's angina or retropharyngeal abscess, (2) direct extension of Pott's disease, and also extension secondary to tuberculosis of the rib or cartilage. Graham⁵ mentioned as a cause rupture of the mediastinal glands and, rarely, empyema. He mentioned edema of the upper part of the chest and swollen veins as important diagnostic signs, likewise, that involvement of the vagus may cause disturbance of the cardiac rhythm, gastric symptoms and vomiting. Graham also considered that the diagnosis of acute mediastinitis is often extremely difficult and can be made only when abscess is present, and that acute inflammation of the mediastinum should always be regarded as a very serious condition with a grave prognosis. Blankenhorn⁶ stated that acute infectious processes of the mediastinum are usually traumatic and,

2 Hare, H. A. *The Pathology, Clinical History and Diagnosis of Affections of the Mediastinum Other Than Those of the Heart and Aorta*, Philadelphia, P. Blakiston's Son & Co., 1889.

3 Dunham, E. K. *Infection in Mediastinum in Fulminating Empyema*, Surg., Gynec. & Obst. **35**: 288 (Sept.) 1922.

4 Gaarde, F. W., in Blumer, George. *Bedside Diagnosis*, Philadelphia, W. B. Saunders Company, 1928, vol. 2, p. 263.

5 Graham, E. A. *Surgical Diagnosis*, Philadelphia, W. B. Saunders Company, 1930, vol. 3, p. 163.

6 Blankenhorn, M. A., in Nelson. *Loose-Leaf Living Medicine*, New York, Thomas Nelson & Sons, 1931, vol. 3, p. 571.

if not promptly fatal, lead to formation of abscesses. The medical aspects of acute mediastinitis are seen in the profound disturbance of the pulse rate, and occasionally of respiration, as a result of vagus and phrenic neuritis.

McLester⁷ stated that mediastinitis occurs, in order of frequency, by extension, metastasis or trauma, and that it occasionally occurs after fracture of the sternum. The prognosis is grave but not hopeless, depending on prompt recognition and surgical intervention. In this connection, Woodroffe⁸ reported 2 cases of traumatic mediastinal abscess in soldiers, with recovery. He was unable to find a report of a single case in the British army during war.

Laryngeal symptoms from pressure on the vagus and recurrent nerves are referred to occasionally as dominating the picture in mediastinitis. In 1875, Johnson⁹ stated that either bilateral spasm or palsy of the larynx may follow. Lemon¹⁰ reported 23 cases with lesions affecting the vagus nerve from the jugular foramen to the arch of the aorta chiefly, with symptoms from involvement of the recurrent laryngeal nerve. Together with Doyle,¹¹ he noted that in 26 cases of Hodgkin's disease with mediastinal involvement, the recurrent laryngeal, vagus and sympathetic nerves escaped direct pressure. No changes in blood pressure were recorded. Gaarde,¹² at the Mayo Clinic, kindly reviewed the blood pressure readings in 64 cases of mediastinal affections, chiefly tumor. Only 2 cases of mediastinal abscess were observed, both with normal readings. Mediastinitis in 11 other cases was associated once with hypertension. Gaarde is under the impression that the total incidence of hypertension in the whole group was no greater than might be expected in any similar age group.

In the absence of special notations as to blood pressure in mediastinal conditions in the available descriptions, it was of interest to note that Villaret¹³ and his co-workers, in 1926, reported in a case of lymphosar-

7 McLester, J. S., in Christian, H. A. *Oxford Medicine*, New York, Oxford University Press, 1932, vol. 2, p. 197.

8 Woodroffe, H. L. W. *Mediastinal Abscess*, Dublin J. M. Sc. **146** 1 (July) 1918.

9 Johnson, George. *On the Laryngeal Symptoms Which Result from the Pressure of Aneurismal and Other Tumours on the Vagus and Recurrent Nerves*, Med-Chir. Tr., London **58** 29, 1875.

10 Lemon, W. S. *Lesions Affecting Vagus Nerve*, M. Clin. North America **7** 293 (July) 1923.

11 Lemon, W. S., and Doyle, J. B. *Clinical Observations of Hodgkin's Disease, with Special Reference to Mediastinal Involvement*, Am. J. M. Sc. **162** 516 (Oct.) 1921.

12 Gaarde, F. W. *Personal communication to the authors*.

13 Villaret, M., and others. *Paroxysmal Attacks of Hypertension in Course of a Lymphosarcoma of Superior Mediastinum*, Bull. et mém. Soc. méd. d. hôp. de Paris **50** 1215 (July 9) 1926.

coma of the superior mediastinum, paroxysmal hypertensive crises and also paroxysmal dyspnea. The main feature in this fatal case of lymphosarcoma in a woman, aged 75, was the occurrence of paroxysmal hypertensive attacks synchronous with severe crises of dyspnea with stridor of from one-half to one hour's duration. Necropsy revealed lymphosarcoma in the superior mediastinum involving the right vagus nerve with pressure in three areas, as shown by careful dissection. The authors considered that vagotonia existed because of slowing of the pulse rate from 110 to 60, and because atropine reduced the dyspnea without much influence on the blood pressure. They considered as incontestable the existence of the transitory hypertensive attacks through mediastinal irritation of the vagus. They noted no similar reference except that of Harvier and Bariety,¹⁴ who reported in a case of carcinoma of the esophagus paroxysmal attacks of loud inspiratory dyspnea associated with arterial hypertension.

Speculation as to the physiologic factors should be briefly considered in view of the increased knowledge of the depressor or aortic nerve, with its receptors in the aortic wall, which transmit impulses that reflexly regulate blood pressure, heart rate and suprarenal secretion. Hering¹⁵ showed that in the rabbit the depressor nerve runs separately, and its excision is followed by a persistent elevation of blood pressure. Starling¹⁶ stated that the depressor nerve in the rabbit is vagus in origin, one root arising from the trunk of the vagus and the other from the superior laryngeal branch of the vagus. In the dog, the depressor nerve runs in the vagus trunk, together with the sympathetic nerve, for the greater part of its course. The sinus nerves, likewise, according to Hering¹⁵ and Koch,¹⁷ exhibit a tonic inhibitory influence on the circulation. Section of the nerves causes pressor effects. Duncan,¹⁸ after anatomic study in man, pointed out that a nerve resembling the isolated depressor in the rabbit is rarely found. Braeucker¹⁹ concluded from his own work and from that of Jonnesco and Ionescu²⁰ that depressor

14 Harvier, P, and Bariety, M. Laryngeal Crises with Cancer of Esophagus, *Bull et mem Soc med d hop de Paris* **49** 176 (Feb 6) 1925

15 Hering H E. Die klinische Bedeutung der Carotissinusreflexe, *Klin Wchnschr* **6** 232 (Jan 29) 1927

16 Starling, E H. Principles of Human Physiology, edited and revised by C L Evans and H Hartridge, ed 5, Philadelphia, Lea & Febiger, 1930

17 Koch, E. Die reflektorische Selbststeuerung des Kreislaufes, in Kisch, Bruno. *Ergebnisse der Kreislaufforschung*, Dresden, Theodore Steinkopff, 1931, vol 1

18 Duncan, D. Anatomy of Depressor Nerve in Man, *Arch Neurol & Psychiat* **21** 1010 (May) 1929

19 Braeucker, W. Der Brustteil des vegetativen Nervensystems und seine klinisch chirurgische Bedeutung, *Beitr z Klin d Tuberk* **66** 1, 1927

20 Jonnesco, Theodore, and Ionescu, D. Experimentelle Untersuchungen, *Ztschr f d ges exper Med* **48** 490 1926

fibers exist in man in two cardiac branches of the sympathetic system and in more than one cardiac branch of the vagus. S. Wright,²¹ in a summary, stated that late evidence is against the emergency-epinephrine-secretion theory of Cannon,²² and favored that of Tournade,²³ whose experiment consisted of drawing blood from the supraclavicular vein of a normal animal into the jugular vein of an animal after supraclavicular sympathectomy. In the recipient, this caused the blood pressure to rise, the arteries to constrict and the rate of the heart to increase. Tournade et al.²³ also showed that this mechanism assisted in steadily maintaining blood pressure, for if the blood pressure is lowered in the donor by hemorrhage, the secretion of epinephrine is increased. Heymans,²⁴ in 1929, found that the secretion of epinephrine is reflexly controlled by the aortic and the sinus nerves. Houssay and Molinelli,²⁵ in 1924, showed that the vagus nerve also contains afferent fibers which can increase the secretion. Wright²¹ stated that these experiments prove convincingly that secretion of epinephrine is reflexly adjusted by means of the aortic and sinus nerves, and that neither the glandular nor the bulbar centers are acted on directly by the level of the blood pressure. At rest, the aortic and sinus nerves seem to exert in the main a tonic inhibitory influence over the activity of the supraclavicular glands. Nathanson's²⁶ observation that minute doses of epinephrine administered subcutaneously release the heart from the depressor effect of the stimulation of the sinus caroticus should be mentioned.

In the rabbit, after excision of the depressor nerve with resultant persistent hypertension, certain pathologic changes, such as thinning of the media and thickening of the intima in the aorta by proliferation, and sclerosis of the pulmonary vessels have been described. Hering¹⁵ pointed out that these arterial changes resemble those occurring after injection of epinephrine, and he was inclined to attribute them, and also the hypertension, in part, to the hyperadrenalinemia following division of the buffer nerves. Wright²¹ raised the question as to what extent hypertension and arteriosclerosis in man may be attributed to the loss of afferent control of the bulbar centers.

21 Wright, S. Lecture on Recent Work on Afferent Control of Circulation in Health and Disease, *Brit. M. J.* **1** 457 (March 12) 1932.

22 Cannon, W. B. *Bodily Changes in Pain, Hunger, Fear, and Rage*, New York, D. Appleton and Company, 1915.

23 Tournade, A., and Chabrol, M. Proof of Reflex Secretion of Epinephrine, *Compt. rend. Soc. de biol.* **92** 418 (Feb. 20) 1925.

24 Heymans, C. Le sinus carotidien isolé et perfusé, zone réflexogène régulatrice de l'adrénalinosecrétion, *Compt. rend. Soc. de biol.* **100** 199 (Jan. 25) 1929.

25 Houssay, B. A., and Molinelli, E. A. Reflex Secretion of Epinephrine, *Compt. rend. Soc. de biol.* **91** 1056 (Nov. 14) 1924.

26 Nathanson, M. H. Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, *Arch. Int. Med.* **51** 387 (March) 1933.

While the connection is remote, the interesting cases of tumor of the suprarenal gland with hypertension should be mentioned. Fishberg and Oppenheimer,²⁷ in 1924, reviewed 15 reported cases of chronic non-nephritic hypertension associated with anatomically demonstrable lesions of the suprarenal glands. Rogers²⁸ reported a case of ganglioneuroma of the suprarenal medulla and postulated imbalance of the vegetative nervous system because of paroxysms of hypertension, disturbance of the carbohydrate metabolism in the absence of a pancreatic lesion, elevation of the basal metabolic rate and gastric disturbances. In addition, it is known that stimulation of the hypothalamus may produce a rise in the blood pressure and secretion of epinephrine. Penfield,²⁹ 1929, described a case of thalamic tumor involving the mesial nuclei in which there were attacks of hypertension.

Physiologically, asphyxia and an excess of carbon dioxide affects the vasomotor center, producing a rise in blood pressure. The asphyxia of carbon monoxide poisoning may produce a rise in blood pressure. Pain or any stimulation of a sensory nerve may cause an acute hypertension. However, the hypertension noted in this case persisted for a greater length of time than any of the possibilities just mentioned, even though they had been operative. Likewise, the cyanosis seen in uncomplicated cases of lobar pneumonia, which may be interpreted as meaning at least a degree of oxygen deficiency and excess of carbon dioxide, is seldom associated with hypertension. In this case, the blood pressure remained elevated after cyanosis had disappeared. Dr. E. T. Bell,³⁰ of the department of pathology of the University of Minnesota, suggested the possibility of involvement of a depressor nerve. Dr. F. H. Scott,³¹ of the department of physiology at the University of Minnesota, considered that involvement of a depressor nerve was possible, but he was inclined to ascribe the effect to mechanical factors.

In view of these physiologic considerations, it appears that this case of hypertension, developing coincidentally with mediastinal abscess, has important implications. While the effect of the vagus in slowing the heart rate was not apparent, the development of hypertension with tachycardia exactly coincident with the development of mediastinitis and mediastinal abscess, and receding following surgical drainage as the process healed suggested, in the absence of renal or other causes, a pro-

27 Fishberg, A. M., and Oppenheimer, B. S. Association of Hypertension with Suprarenal Tumors, *Arch Int Med* **34** 631 (Nov) 1924.

28 Rogers, E. Paroxysmal Hypertension Associated with Ganglioneuroma of Suprarenal Medulla, *Am Heart J* **8** 269 (Dec) 1932.

29 Penfield, W. Diencephalic Autonomic Epilepsy, *Arch Neurol & Psychiat* **22** 358 (Aug) 1929.

30 Bell, E. T. Personal communication to the authors.

31 Scott, F. H. Personal communication to the authors.

found change in the vasomotor regulatory mechanism. In view of the lesion which, according to Braeucker,¹⁹ anatomically could have involved the course of the afferent aortic nerves, a rational explanation on consideration of physiologic and pathologic data may be postulated. These data consist of the established importance of the afferent buffer or depressor nerves which assist in maintaining normal blood pressure through tonic inhibitory influence on the bulbar centers through control, in part, of suprarenal secretion. Its proved involvement in one case¹³ of neoplasm was associated with transient attacks of dyspnea and hypertension. In another case of carcinoma of the esophagus, involvement of the recurrent nerves was associated with similar transient attacks of hypertension and dyspnea.

It appears, therefore, entirely possible that fibers of the afferent buffer mechanism were directly involved in the area of the suppurative mediastinitis. If new conceptions of the mode of action of the depressor nerves are considered, the physiologic mechanism includes the increase in secretion of epinephrine.

SUMMARY AND CONCLUSIONS

A case is reported in which, following fracture of the sternum, pneumonia, mediastinitis and mediastinal abscess developed and were recognized in sequence. Coincident with suppurative mediastinitis and pointing of abscess through the line of fracture to the subcutaneous tissues, an acute hypertension developed. This was not associated with renal or other previously recognized or recorded provocation. Simultaneous elevation of the pulse rate in the presence of lower temperature indicated a profound alteration in the vasomotor regulatory mechanism.

In view of the unique nature of this case, speculation as to the etiology was in order. On the basis of physiologic considerations and anatomic relations, the possibility is here suggested that the mediastinitis and abscess involved the depressor nerves, approximating the effect of a total resection with the resultant hypertension seen in experimental animals. Mechanical effects cannot be ruled out as a cause, although in the literature reviewed, mediastinal neoplasms causing decided pressure were not found to precipitate hypertension, except in one instance of neoplastic involvement of the right vagus nerve.

We believe that an additional precipitating cause of acute nonrenal hypertension has been recorded with the report of this case.

Students' Health Service

News and Comment

CENTRAL SOCIETY FOR CLINICAL RESEARCH

The seventh annual meeting of the Central Society for Clinical Research will be held in the Tropical Room of the Medinah Club, 505 North Michigan Avenue, Chicago, on Friday, November 2, and Saturday morning, November 3

The Central Society for Clinical Research was founded and organized largely through the initiative and energy of Dr Frank Billings. It was his desire to establish a society which would be a common meeting place for the younger physicians in the cities and villages of the Middle West and which would serve to maintain their interest in scientific medicine and clinical research. He lived to see assured the success of the society in which he was so interested. The meetings are open to all.

Book Reviews

Obstetric Medicine Edited by Fred L. Adair, M.D., Professor of Obstetrics and Gynecology, University of Chicago, and Edward J. Stieglitz, M.D., Assistant Clinical Professor of Medicine, Rush Medical College of the University of Chicago Price, \$8 Pp 743, with illustrations Philadelphia Lea & Febiger, 1934

As the editors state, this book is an effort to coordinate and correlate the medical knowledge concerning the problems of diagnosis, therapy and prognosis of disease occurring coincidentally with pregnancy. It is written by thirty-nine well known contributors under the editorship of two.

It is a fairly good textbook of medicine. To be sure, it treats of many conditions that appear to have little to do with ordinary pregnancy, for example, African sleeping sickness and *Schistosoma japonicum* "endemic in Japan, the valley of the Yangtze River in China, in the Philippine Islands, Singapore, and the Shan States." But the book in general is modeled on standard lines. The infectious diseases and the various systemic disorders, including diseases of the teeth, eyes and skin, are competently discussed. The blood and the endocrine glands receive adequate consideration, and there is an excellent chapter on deficiency disease as related to pregnancy, while allergy and industrial poisoning, as well as drug habits, receive an appropriate amount of attention. The commendable feature of the volume lies in the imagination behind it, for a reference book of this sort should be of great value, the disadvantage is that in its present form the book is neither a particularly first class textbook of obstetrics on the one hand, nor a particularly first class textbook of general medicine on the other, but a somewhat unconvincing mixture.

Die Tonuskrankheiten des Herzens und der Gefasse By Professor J. Pal Price, 18 marks Pp 228, with 20 illustrations Vienna Julius Springer, 1934

This monograph deals with various problems concerned in the regulation of blood pressure. After an introductory chapter, hypertension is discussed at considerable length. The author recognizes two kinds of hypertension: transitory hypertension from vascular spasm and permanent hypertension in part due to heredity and in part acquired, as time goes on, from a variety of causes. He gives an excellent description of the changes which may occur from hypertension in the large vessels, in the retinal vessels and in the capillaries and discusses methods of treatment, using illustrative reports of cases to enliven his thesis.

Hypotension is taken up in much the same manner. Hypotension is considered as being either congenital or acquired, what may be done in the treatment of low blood pressure is described.

The book is interestingly put together and is written from a combined clinical, pathologic and physiologic point of view. It contains an excellent list of references to current literature. On the whole, this work is well worth reading and will prove especially valuable to clinicians interested in vascular disease and its management.

Stoffwechselprobleme By S. J. Thannhauser Berlin Julius Springer, 1934

This small book contains five lectures on the following topics: (1) the structure of nuclear material in plants and animals and the metabolism of nucleins, (2) the chemistry of the pigments of the blood and bile, (3) the place of formation of biliary pigment, (4) the production of icterus and (5) the lipoidoses: xanthoma, Gaucher's disease and Niemann-Pick's disease.

The presentation is scholarly and critical, each lecture contains a review which brings the subject up to date by including the more recent contributions. Thannhauser is professor of medicine in Freiburg. He speaks with special authority in the fields of purine chemistry and bile. His "Lehrbuch," a monograph on metabolism and diseases of metabolism, is widely recognized as a masterpiece of medical writing in this field. The "Stoffwechselprobleme" is lacking in a bibliography, much to the disappointment of the reviewers.

Traité de physiologie normale et pathologique Tome VII Sang et lymphe, réactions d'immunité Deuxième édition. Published under the direction of G.-H. Roger and Leon Binet. Price, Stitched, 100 francs, bound, 120 francs. Pp 731, with 82 figures. Paris: Masson & Cie, 1934.

This treatise on physiology in eleven volumes has been so well received that it has been considered worth while to bring out a second edition. The present volume is the first of this edition that has appeared. It is considerably (229 pages) longer than the first edition. The following subjects have been particularly revised and amplified: the origin of the formed elements, hemorrhage, transfusion, blood chemistry, coagulation, immunity and anaphylaxis. The work is liberally documented with references to the literature, mostly French, although English, American and German works are cited as well. French science may well feel proud of this evidence of its vitality.

Reliefstudien an der normalen und Krankhaft veränderten Speiseröhre
By Richard Schatzki. Pp 149, with 159 illustrations. Acta radiologica, Supplementum XVIII, 1933.

This interesting monograph deals systematically with the roentgen appearance of various lesions of the esophagus. There are 159 reproductions of roentgenograms. These serve to illustrate the text, which deals not only with interpretation but with technic as well. There is a thorough bibliography.

Brucella Infections in Animals and Man. Methods of Laboratory Diagnosis By I. Forest Huddleson. Pp 108. The Commonwealth Fund, 1934.

This little monograph brings together in an interesting manner the available literature on the bacteriology of the Brucella group and deals especially with the methods of laboratory diagnosis. The technic of isolation of the organisms, the pathology of experimental infection and the biologic methods for identifying and separating various strains are described. The bibliography includes one hundred and eighty-eight titles, the illustrations are good, and there is an index.

Radiologie de la vésicule biliaire By Nemours-Auguste. Price, 45 francs. Pp 186, with 102 figures and 27 plates. Paris: Masson & Cie, 1934.

This book is in line with the French custom of monographic treatment of highly restricted subjects. One would hardly think that there was enough to say about the roentgenology of the gallbladder to fill a whole volume, and still one finds here surprisingly little superfluous matter. The subject is taken up from every possible angle. Especially valuable are the numerous excellent reproductions of roentgenograms and diagrams. The book should prove a storehouse of information not only for roentgenologists but also for physicians in general. There is a thorough bibliography, with good representation of the American literature.

ERYTHEMA ARTHRITICUM EPIDEMICUM (HAVERHILL FEVER)

EDWIN H PLACE, M D

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AND

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In January 1926 a small but explosive outbreak of illness occurred in a restricted area of Haverhill, Mass. Several physicians called by patients in this epidemic were struck by its unusual features, especially the abruptness of the onset, the peculiar eruption and the marked involvement of the joints.

On January 22 we were called in consultation by the department of health. A preliminary report was made in February 1926.¹ A complete bacteriologic report was made by Parker and Hudson² in September 1926. The present paper is a complete report of the findings in this epidemic.

The only previous epidemic of a disease similar to this of which we have found a record occurred in May and June 1925, at Chester, Pa. Studies of this outbreak were made by Dr. Charles Armstrong³ and Dr. Harold B. Wood,⁴ state epidemiologist. In that epidemic about 400 cases were discovered in May and June 1925. It is estimated that about 600 cases occurred with no deaths. Although the nature of the epidemic was not determined, there was a striking similarity of onset, symptoms and course and epidemiologic relation to the milk supply to the disease reported here.

The onset was unusually abrupt, with severe chills, fever, vomiting, headache and pains in the back and joints. There was a remission of fever after a few days. The rash appeared at varying times in the early period of the disease as a macular or papular and often petechial eruption on the wrists, arms, feet and ankles. In a few cases it became pustular. The white blood cell count varied in 6 cases from 6,000 to 15,000. The joints were painful and tender, in some cases showing

From the South Department, Boston City Hospital

1 Place, E. H., Sutton, L. E., and Willner, O. Erythema Arthriticum Epidemicum, Preliminary Report, Boston M. & S. J. **194**:285, 1926

2 Parker, Frederick, Jr., and Hudson, N. Paul. The Etiology of Haverhill Fever (Erythema Arthriticum Epidemicum), Am. J. Path. **2**:357 (Sept.) 1926

3 Armstrong, Charles. Milk-Borne Outbreak at Chester, Pa. Report rendered July 18, 1925, personal communication

4 Wood, Harold B. Personal communication to the authors

no local signs, but in others swelling and occasionally redness. Pain and stiffness in the joints persisted after the subsidence of fever.

Although dengue was the working diagnosis during the early part of the epidemic, a study of the mosquitoes showed no unusual number and none at all of *Aedes aegypti*.

It was soon found that the milk supply was responsible. Ninety-two per cent of the known patients received raw milk from a bottling plant in the city. About 20 per cent of the persons receiving milk from this source had the disease as compared with 0.5 per cent of the population as a whole. In 250 homes in which the disease occurred there were 1,194 persons, 33 per cent of whom had the disease. Of the 8 per cent of patients not receiving milk from the bottling plant nearly one half had taken the infected milk in restaurants, leaving only 4.5 per cent of the known cases which were not definitely traceable to the milk. On one of the six farms supplying milk to the bottling plant was found the first person known to have had the disease. This person became ill four days before the first customer to contract the disease became ill. In the first six days after the onset of the first case 5 other cases appeared, including that of one of the proprietors of the bottling plant. Shortly afterward the outbreak became explosive.

From a few observations the period of incubation in the Chester epidemic was believed to be from two to four days.

Two blood cultures in the acute stage were negative. Forty-two per cent of throat cultures from 38 patients were positive for streptococci. Of 18 patients still more or less ill with sore throat, streptococci were found in 61 per cent, and in 31 per cent of 13 who had recovered. Of 7 persons who had not been ill, 14 per cent had positive streptococcus cultures. There was considerable variation in the hemolyzing power of the streptococci isolated.

A definite decision as to the nature of the disease was not made for opinions varied from dengue fever to streptococcic sore throat.

Levaditi, Nicolau and Poincloux⁵ described an infection in one of their co-workers which clinically resembled this disease, and an organism, *Streptobacillus moniliformis*, which appears to have been the etiologic agent, was isolated from the blood during the acute stage. It has characteristics similar to those of the organism isolated in the Haverhill epidemic. Their report is of a single case occurring in March 1925 with recovery.

Earlier than that we have not found any report of a clinical entity with bacteriologic findings which resemble those in the Haverhill epidemic.

⁵ Levaditi, C., Nicolau, S., and Poincloux, P. On the Etiologic Role of the *Streptobacillus Moniliformis* in Acute Septicemic Polymorphic Erythema, *Compt rend Acad d sc* **180** 1188, 1925, Research on the Etiology of an Acute Polymorphic Erythema. *Presse med* **34** 340 (March 17) 1926.

In 1932 Hazard and Goodkind⁶ reported a case in which Haverhill fever was diagnosed in the wards of the Boston City Hospital, with recovery from the blood at three different times of an organism of the same characteristics as that isolated in the Haverhill epidemic.

Levaditi, Selbie and Schoen⁷ recently reported the isolation of *Streptobacillus moniliformis* (Levaditi) from mice ill with spontaneous polyarthritis.

In a number of cases of fever following the bite of a rat organisms have been obtained from the blood similar to and possibly identical with *Haverhillia multiformis* by Schottmueller,⁸ Blake,⁹ Litterer,¹⁰ Tunncliffe and Mayer,¹¹ Ebert and Hesse¹² and Mackie and McDermott,¹³ although the latter later found a spirillum on inoculation of animals.

THE ETIOLOGIC ORGANISM IN THE HAVERHILL EPIDEMIC

In the Haverhill cases an organism was found by Parker and Hudson² in blood cultures taken by us in 11 of 17 cases and in fluid aspirated by us from the knee joints in 2 cases. They named the organism *Haverhillia multiformis*, thereby making a new genus *Haverhillia* in the family *Mycobacteriaceae* (Chester) in the order *Actinomycetales* (Buchanan). Serum from the patients produced agglutination of a polyvalent antigen of this organism in from 1:50 to 1:100 dilution, while serum from normal persons failed to show agglutination in dilutions higher than 1:20. Skin tests with the organism were positive in 15 of 18 cases from four to five months after the infection and negative in 10 controls.

6 Hazard, J. B., and Goodkind, R. Haverhill Fever, Report of a Case and Bacteriologic Study, *J. A. M. A.* **99** 534 (Aug. 13) 1932.

7 Levaditi, C., Selbie, F. R., and Schoen, R. Arthritis of Spontaneous Polyarticular Rheumatism of the Mouse Produced by *Streptobacillus Moniliformis*, *Compt. rend. Soc. de biol.* **103** 1193 (May) 1930. Levaditi, C., and Selbie, F. R. Mode of Transmission of Acute Polymorphic Multiforme Erythema, *Compt. rend. Acad. d. sc.* **189** 1332, 1929.

8 Schottmueller, H. Etiology and Clinical Characteristics of Rat-Bite Fever, *Dermat. Wchnschr. (supp.)* **58** 77, 1914.

9 Blake, F. G. The Etiology of Rat-Bite Fever, *J. Exper. Med.* **23** 39 (Jan.) 1916.

10 Litterer, William A. New Species of *Streptothrix* Isolated in a Case of Rat-Bite Fever, *J. A. M. A.* **68** 1287 (April 28) 1917.

11 Tunncliffe, Ruth, and Mayer, K. A Case of Rat-Bite Fever, *J. Infect. Dis.* **23** 555 (Dec.) 1918.

12 Ebert, B., and Hesse, E. On the Clinical Appearance and Bacteriology of the Japanese Rat-Bite Fever, *Arch. f. klin. Chir.* **136** 69, 1925.

13 Mackie, T. J., and McDermott, E. N. Bacteriology and Observations in a Case of Rat-Bite Fever. *Spirillum Minus*, *J. Path. & Bact.* **29** 493 (Oct.) 1926.

Koch's postulates were not proved as there was no experimental inoculation of man, but it is felt that the evidence of the organism found in the blood stream and pathologic lesions, properly controlled, as well as the appearance of immune bodies in the infected patients is sufficient for regarding this bacterium as the etiologic agent

EPIDEMIOLOGY

Haverhill is a manufacturing city. At the time of the epidemic it had a population of 35,000. On Jan 22, 1926, twenty days after the appearance of the first case, the local board of health was notified by a local physician who had seen personally 8 cases that day. Up to that time there had been 71 cases. The following day the survey for the

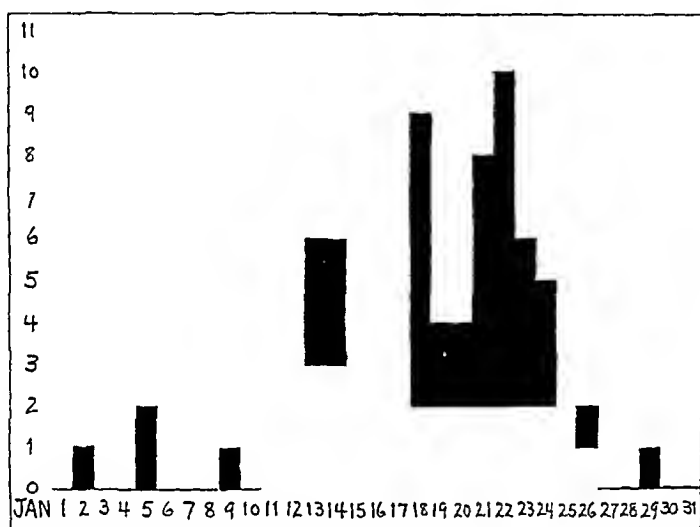


Fig 1—A graph showing the chronological occurrence of cases

epidemic was begun. From then on 15 cases appeared before the epidemic was stopped. Three cases appeared during the first week, 31 during the second and 37 during the third. The epidemic reached its height at the end of the third week. Figure 1 shows the chronological incidence.

The epidemic was limited to a small district bordering the river, rectangular in shape, measuring about 5,000 by 1,500 feet (1,500 by 500 meters), including two roughly parallel streets and the short intersecting ones. Within this area 86 cases developed (fig 2). The patients were chiefly of foreign extraction, Lithuanians, Italians, Poles and Jews (in the order named as to frequency) appeared to be the chief inhabitants of the infected district.

Thirty-nine families were involved, and 21 of these had more than 1 case. In a family of 18, including the grand-parents, parents and children, there were 10 cases, the largest group in any family.

The ages of the patients varied from 8 months to 54 years. No nursing babes were among those infected. The age classification was

	Number	Per Cent
Under 2 years	7	8.2
2 to 12 years	31	36.0
12 to 21 years	17	19.8
21 to 54 years	31	36.0

Fifty-one, or 59 per cent, of the patients were females and 35, or 41 per cent, were males.

Almost all of the men were occupied in shoe factories and in the neighboring provision stores.

The living conditions of the homes were from poor to moderate, with the majority of the homes clean and neat. Every house had an inside toilet, there were no outside privies. The kitchen was the most

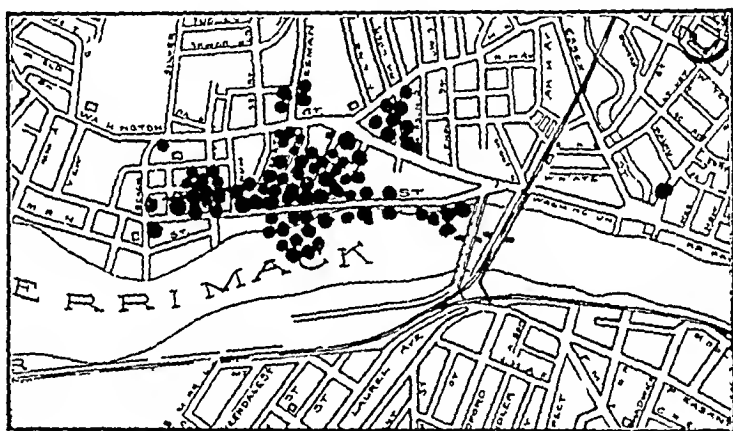


Fig. 2—Map of Haverhill, Mass., showing the distribution of cases. Each case is represented by a dot.

used 100m in most of the homes, and in some homes in which the conditions were poor there were many sleeping in a room. As a whole most of the rooms showed plenty of light and sunshine. Rats were present in a few of the houses, but no vermin were found. Flies and mosquitoes were not present, as the epidemic appeared in January, and there was much snow.

Running water was supplied in every house from the city reservoir. The city health department reported that nothing had happened to the city's water supply recently to suggest that the water might be contaminated, and no cases had occurred in other parts of the town using the same water supply.

The food supply was obtained from the neighboring provision stores. The majority of the patients, except the infants, stated that they had eaten raw food lately, such as lettuce and occasionally celery. Raw

meat was eaten by 1 patient, but the rest claimed that their meat was always cooked. Fruits such as apples, oranges, bananas and pineapples were eaten by many.

The milk supply in every case came from one dairy either directly or through four stores in which this dairy's milk was sold. One patient, however, ate only ice cream made from this milk. The entire milk supply of this dairy was distributed to a small area of the city which corresponded to the area of the disease. The distributor daily supplied 18 quarts (19 liters) of milk directly to eleven residences and 62 quarts (65 liters) to four stores, which accounted for the dairy's entire supply.

Of the 39 families presenting cases of the disease 25 secured milk from stores supplied by this dairy alone, and 6 took milk from stores supplied by this as well as other dairies. The other 8 families had delivery of milk from the dairy in question direct to the home.

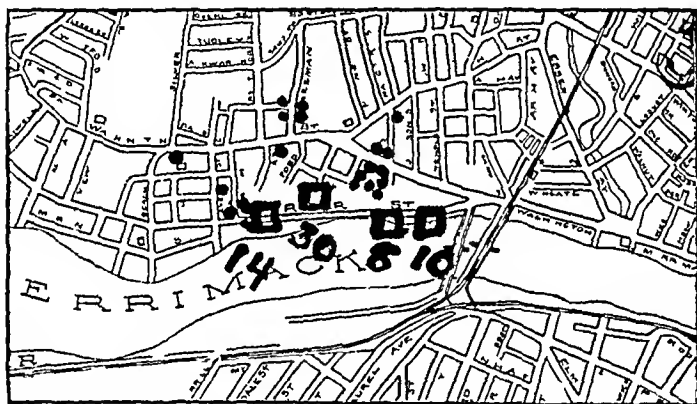


Fig 3—Map of Haverhill, Mass., showing the distribution of milk carrying the infection. Each dot represents a family taking milk directly from the dairy. The squares represent stores, with the number of quarts received by each in the adjacent figures.

Two hundred and thirty-one persons were included in the group, of whom 84, or 36 per cent, had the infection, an average of 2.1 cases per family. In several of the families some members rarely or never drank milk, and these usually escaped infection. In several only the persons who drank milk contracted the disease. Two cases occurred in families not receiving milk from the dairy, but both patients had partaken of the milk in homes having this supply. One woman using milk from the suspected dairy always boiled it, and she remained well.

The milk was ordered pasteurized on January 27, and after that only 1 case developed, two days later. The patient gave the history of having drunk the milk unpasteurized.

No cases developed through contact. Every patient gave a history of the ingestion of milk or its products. In some families there were

several sleeping in a room, but no case occurred through contact. None of the medical staff working in the field, hospitals or laboratory had the disease, even though it was impossible to carry out perfect aseptic technique.

In 17 cases in which there was some soreness of the throat, cultures were taken at varying times from the first to the twenty-seventh day of the disease. No unusual organisms were found. The usual flora of the mouth was present, including staphylococci, pneumococci, streptococci, etc.

The dairy was located several miles outside the city, and the milk was hauled to the customers every morning. Twelve cows were maintained, none of which was ill. One cow freshened from one to two months before the beginning of the epidemic, and her milk was added four or five days later. To make up a supply of 80 quarts (84 liters) two cans were received daily from two other dairies nearby. Examination of the herds by the city veterinarian gave negative results, and cultures from the milk proved negative. The water supply was from two wells.

The residents of the farm were the dairyman, his wife and 6 children, varying in age from 1 to 20 years. Within the past six months there had been no history of illness in the family, and an examination gave negative results. They stated that they used the milk. The sanitary condition of the dairy was as good as could be expected, but there was little modern equipment. Pasteurization was not done, as the saving of the expense of pasteurization allowed the milk to be sold 1 cent cheaper than that of the competitors. By the time the milk was pasteurized the epidemic had nearly ceased, as almost every customer who continually drank the milk had had the disease.

The portal of entry is thought to be intestinal. The only two epidemics reported have been shown to have been due to the ingestion of milk. The absence of cases through contact tends to exclude the respiratory tract as a portal of exit.

The disease appeared both in January and in June, making insect or seasonal factors apparently of little import.

During the epidemic in Haverhill we carried blood bouillon cultures by motor 35 miles (56 kilometers) to Boston in freezing weather without destroying the organisms. The blood did not freeze, however.

PERIOD OF INCUBATION

The time of ingestion of the infected milk in relation to the onset could not be told in most cases as the milk from the same dairy had been used continually. In 3 cases the partaking of the infected milk preceded the symptoms one, two and from two to three days respectively.

In one of these cases a woman, 28 years old, who nursed in the household of a friend, took milk on January 21 and 22. Symptoms developed on the night of January 22. She took none of the infected supply elsewhere. In a second case a baby, 8 months old (who was at first believed not to have taken the milk), visited with her mother, and partook of the infected supply on January 21 and 22. She became ill on January 23. In the third, a man, 22 years old, came from a Boston hospital on the night of January 25 to nurse his father in the twelfth day of illness. He drank milk on January 26 and 27, the disease developed on January 29. This milk was pasteurized after January 27.

It is probable that the period of incubation varies with the amount of organisms ingested.

SOURCE

The source of infection is obscure. The causative organism had been previously noted only once, and that was not known to us at the time. It may have secured entrance to the milk from bovine sources, although its poor growth in milk makes the udder improbable as a focus. One cow showed antibodies in the blood, but routine examination revealed only a slight superficial lesion of one teat and dripping from another. On a visit to the dairy after agglutinins were discovered in her blood, it was found that this cow alone had been disposed of.

Contamination of the milk from water or handling through contaminated vessels is possible, as no sterilization was done, the simple equipment for that purpose being out of order at the time. Contamination from fodder such as ensilage has not been excluded.

The work of Levaditi and his co-workers and of Strangeways¹⁴ showed that mice, and especially rats, are the natural carriers of *Streptobacillus moniliformis*. Levaditi, Selbie and Delorme¹⁵ showed that the infection in mice with multiple arthritis or septicemia may be conveyed to other mice if kept together in the same jar in the dark, but not if kept in the light. They found the organism in the urine in the bladder, and believed that the infection is spread by the contamination of food in this manner as well as by bites. Strangeways found *Streptobacillus moniliformis* in the nasopharynx of 50 per cent of rats bred in the laboratory and in four wild rats, but not in the blood or organs. A study of the rats and mice at the dairy was not made, but the possibility of this source is intriguing.

14 Strangeways, W. J. Rats and Carriers of *Streptobacillus Moniliformis*, J Path & Bact **37** 45 (July) 1933.

15 Levaditi, C., Selbie, F. R., and Delorme, M. Mode of Spontaneous Transmission of Infectious Polyarticular Rheumatism Caused by *Streptobacillus Moniliformis*, Compt rend Soc de biol **107** 501, 1931.

The identity of *Streptobacillus moniliformis*, *Streptothrix muris-ratti* and *Haverhillia multiformis* requires further study, but at present they show too little difference to suggest more than different strains. Levaditi found that *Streptobacillus moniliformis* of human source grew in milk, and that rabbits were the most susceptible animals, while the strain from mice was much more virulent for mice than for rabbits.

If the evidence of the short period of incubation can be accepted the milk supply must have been repeatedly or continually infected for a period of over three weeks.

CLINICAL PICTURE

Onset—The onset in most cases was acute. Rarely, there was an indefinite history of malaise, of pain in the extremities and of headache gradually appearing in the course of a couple of days. Most gave the history of being perfectly well until suddenly a chill, vomiting or a severe headache ushered in the illness. In many cases the onset was extraordinarily abrupt, the patient being seized by a sudden violent chill while at work or asleep. In some cases a sudden and severe headache, vomiting, prostration and malaise interrupted their daily routine. Convulsions occurred in infants or very young children.

The fever tended to show a remission to normal in from two to five days and the symptoms were so ameliorated by the third or fourth day that many of the patients got out of bed, and several started back to work, to return to bed later with the recurrence of fever. The fever recurred two or three days after the remission to normal, the recurrence coinciding with the onset of generalized involvement of the joints. The eruption began usually during the primary fever, but tended to persist or even to increase into the relapsing period.

The chief symptoms of the 86 patients and their appearance during the first stage of the disease were

	Number	Per Cent
Fever	83	96.5
Vomiting	53	61.6
Headache	48	55.8
Chills	47	54.7
Chilliness	11	12.8
Dizziness	14	16.2
Somnolence	7	8.1
Irritability	4	4.6
Herpes	4	4.6
Backache	4	4.6
Delirium	4	4.6
Epistaxis	3	3.5
Nausea	3	3.5
Convulsions	2	2.3
Anorexia	2	2.3
Photophobia	1	1.1
Tingling and numbness	1	1.1
Shooting pains	1	1.1

Fever—Every patient examined during the acute stage showed fever, either slight or a temperature as high as 105 F. The 3 patients reported as free from fever were without records of temperature.

The typical temperature curve was a sudden rise following a chill or chilliness, its height being reached within twenty-four hours. A drop in temperature to normal occurred almost as rapidly, in from twenty-four to forty-eight hours in most cases. When chilliness persisted, the temperature remained up. The symptoms abated as the

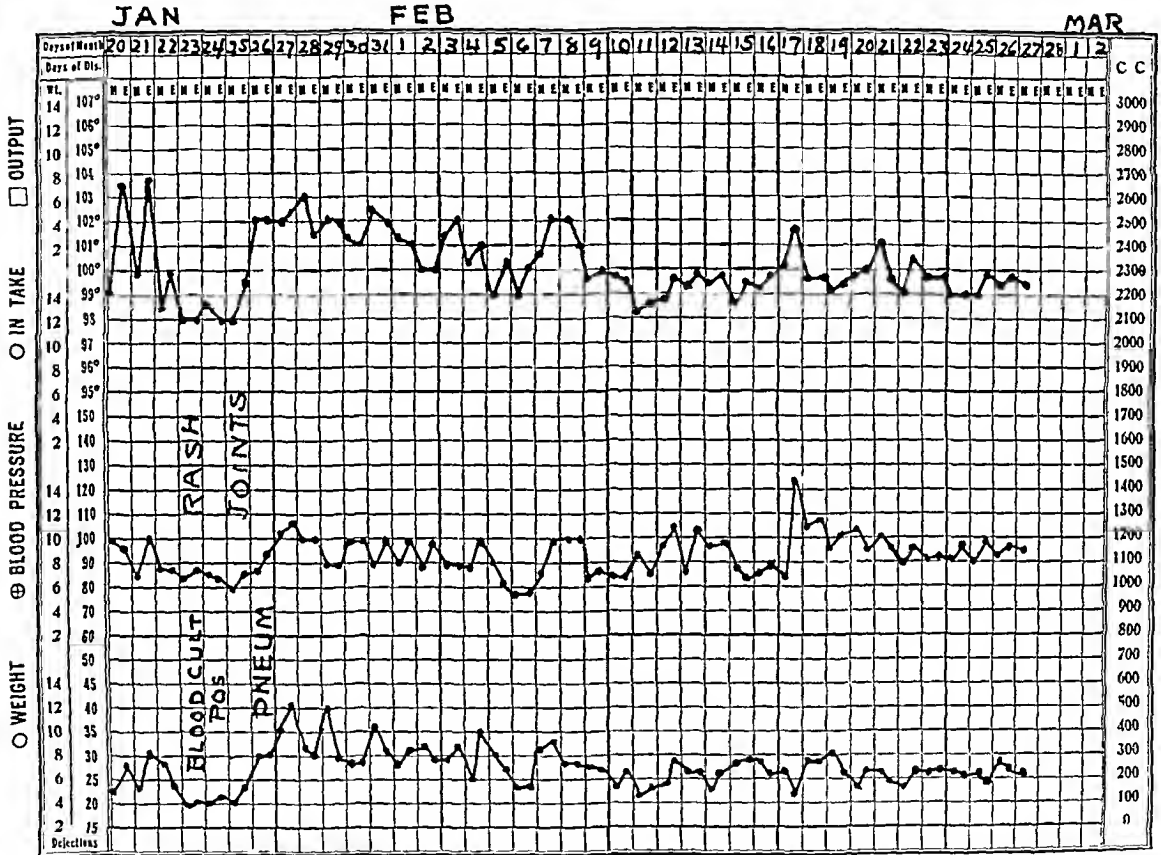


Fig 4—A characteristic temperature curve in a woman, aged 44, from the first day

temperature fell. In some cases in which the stages merged the elevation of the temperature persisted at a lower level. As a rule when the rash appeared the temperature was either normal or nearly normal.

When the second stage set in the temperature was elevated and remained so for a few days or weeks, depending on the severity of the arthritis. Few of the patients showed no rise of temperature with a somewhat mild arthritis, others had a temperature as high as 103 F and throughout several weeks averaging about 100 F. The majority of the fevers, however, were septic, the temperature gradually reaching normal in about a week.

Pulse and Respiratory Rates—The pulse rate varied with the patient. It showed no marked relative increase or decrease, but varied with the temperature. The respiratory rate showed nothing abnormal. There was an increase in those patients who showed pneumonic conditions in relation to the amount of pathologic change.

Vomiting—This occurred in 61 per cent of the cases. In a little over half of these vomiting occurred more than once, averaging three or four times. In the severe cases retching was present, with bile-

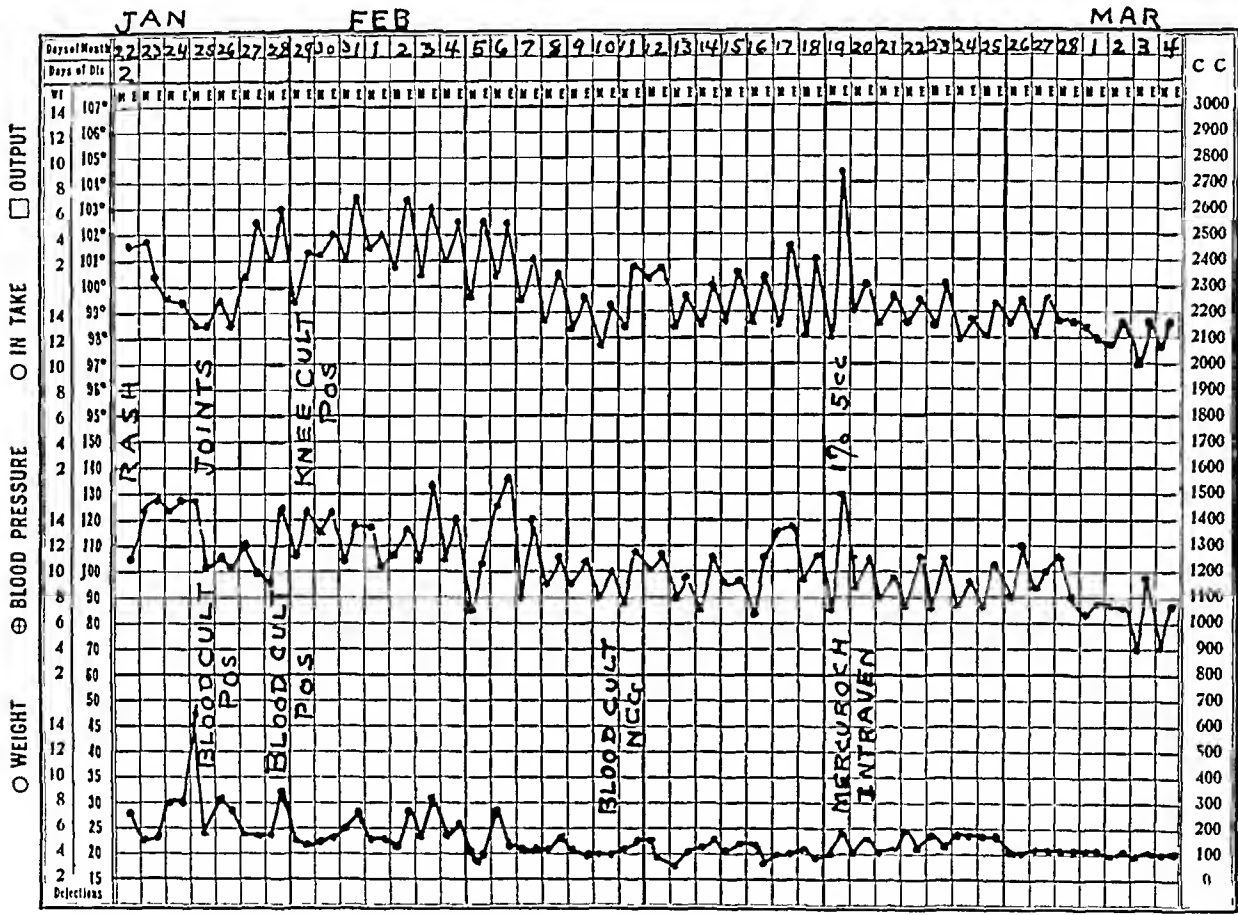


Fig 5—A characteristic temperature curve in a girl, aged 13, from the second day

stained vomitus. One patient stated that he vomited “pure blood.” Vomiting occurred over two days and from three to eight times in 7 per cent of the patients. One patient, a girl of 5 years, vomited thirty times over a period of three days. A small percentage ($3\frac{1}{2}$) of the patients did not vomit, but showed nausea.

Anorexia was present in 2 patients who did not show nausea or vomiting, and was more or less evident in all cases.

Chills—Definite chills occurred in 55 per cent of the cases (2 patients stated that their teeth were almost shaken out), and, when present, generally were the first symptom. As a rule, they lasted for

fifteen or twenty minutes, several patients claiming chills of a duration of one half hour. A few had repeated chills over a period of two days, and 1 for three days. Cyanosis was marked in 2 infants of the same family, aged 10 months and 2 years. The former had seven definite chills over a period of two days, and the latter had six during the same time. Thirteen per cent showed chilliness, but not marked enough to be classified as chills. The chilliness was of one, two or three days' duration, and in 1 case one week.

Convulsions were present in 2 children, aged 3 and 5, who did not have definite chills. In the former there was one convulsion which lasted for fifteen minutes, the other had two attacks of about the same duration.

Headache and Other Like Disturbances—This occurred in 56 per cent of the cases, and was fairly severe. As a rule the headache was generalized, but when limited it was in the frontal region. The duration of the headache varied from an hour to a week, but in the majority of cases the duration was from twenty-four to forty-eight hours.

Dizziness was present in 16 per cent, occurring in the severer cases and lasting through the height of the toxic symptoms. Somnolence was complained of by 8 per cent, mostly adults. One patient, unable to sleep for three days, was afflicted the most. Restlessness and irritability were found in the infants and small children in a few cases. Severe backache was present in 4 patients. The rest showed more or less general malaise. The sicker patients showed prostration. Delirium occurred in 4 cases, in 2 uncomplicated cases at the onset, in another on the fifth day of the disease, and in the fourth in complicating pneumonia which developed five days after the onset.

Photophobia was complained of by 1 adult, who also had blurred vision for twenty-four hours. Tingling and numbness of the right hand occurred in 1 adult on the second day of the disease, and lasted for several days. Stabbing pain, like needles, in the elbows shooting down the arms to the wrists persisted for two days in another adult. Herpes simplex labialis was present in 4 patients.

Epistaxis—This occurred in 3, but was of slight degree.

Rash—The eruption appeared anywhere from the first to the fifth day of the disease. In 1 case the eruption appeared as late as the eighth day. In 7 cases the eruption appeared on the day of onset, in 16 on the second day, in 3 on the third, in 10 on the fourth, in 7 on the fifth and in 1, as previously mentioned, on the eighth day. In almost one-half the cases it appeared on the third day, when the temperature usually returned to normal.

It was most marked at the distal ends of the extremities, especially on the lateral or extensor surfaces and occasionally with accentuation

around the joints. Frequently it extended down the backs of the hands and the dorsa of the feet and less frequently over on the palmar and plantar surfaces. In the severer cases the exanthem was not limited to the extremities, but was present on the forehead and the sides of the face and on the trunk, usually the chest and the back. The flexor surfaces of the body were usually free except in marked eruptions, when there was extension from the extensor surfaces.

The eruption showed blotchy, irregular, generally rounded, maculopapular, dull red lesions varying greatly in shape and arrangement, measuring from 1 or 2 to 3 or 4 mm in diameter. In a few cases the lesions were larger, particularly when present on the face. In 1 case a few lesions measured almost 1 cm in diameter. The rash varied in



Fig 6—Photograph showing the subsiding eruption on the fifth day, eight days after the onset of the disease

type, being chiefly rubellaform, but in some cases tending toward morbilliform. The lesions showed no tendency to clear in the centers; they faded on pressure and on the whole were discrete except for an occasional small area of conglomerate lesions around the joints.

The eruption increased in intensity for from one to three days, and lasted from one to fourteen days. The average duration was six days. In the mildest cases the eruption was present for one day. In 1 case it lasted for three weeks. In the persisting eruptions pigmentation generally resulted lasting from two to three weeks.

Petechial hemorrhages were present along the dorsa, the inner aspects and the plantar surfaces of the feet in the most toxic cases. A few patients showed some over the lower part of the leg and lower part of the arm which remained for some time after the erythema had faded.

A tourniquet applied to the upper part of the arm produced hemorrhages in the lesions of the lower part of the arm within five minutes after its application. Hemorrhages and pigmentation were present in about 21 per cent of cases.

Fine desquamation appeared in 20 per cent of the cases. It was found along the distal end of the lower part of the arm and leg, and in several cases was profuse on the hands and feet, including the fingers and toes. It was present after the fading of the eruption, but accompanying the pigmentation. Pigmentation, hemorrhage or desquamation occurred only after an erythema stage.

The exanthem was recognized in 80 of the 86 cases, or 93 per cent. Since the presence of rash in some instances was determined by the history, it is probable that some rashes may have been overlooked, judging from the mentality of some of the patients. An eruption was present in all cases that were observed personally from the beginning of the disease. The distribution of the eruption in 80 patients, or 93 per cent, was as follows:

	Patients	Per Cent
Trunk, face, arms and legs	9	
Trunk, arms and legs	4	
Trunk and arms	1	
Face, arms and legs	26	
Arms and legs	25	
Face and arms	5	
Arms	8	
Legs	4	
Totals		
Trunk	15	17.4
Face	40	46.5
Arms	76	88.4
Legs	65	75.6

Arthritis.—This was the most persistent symptom. Its onset was from the second to the thirteenth day of the disease, and usually marked the beginning of the recurring fever. In the average case involvement of the joints began on the fourth or the fifth day of the disease. In almost all cases it was multiple, and in over half there were more than six joints involved. There were many remissions and recurrences. In addition to definite involvement of the joints there was generalized pain in the arms and legs with no local evidence in the joints. Some, chiefly infants and children, showed no definite involvement of the joints. About 16 per cent had generalized pain, of whom three fourths were infants and children. The vertebral joints were possibly involved, as there was great pain in turning or moving the neck or back.

Objectively the joints varied from a normal appearance to well marked swelling and slight redness. In the knee joint in at least 6 cases fluid was demonstrated by a floating patella. The joints were

exceedingly painful crippling the patients, keeping them either in bed or in the house, and dominating the relapsing stage of the disease. Table 1 shows the extent of involvement of the joints in 83 patients.

In the epidemic in Chester, Pa., 1 patient complained of pain on moving the eyes.

TABLE 1—*Joint Involvements*

Joints	Pain	Swelling	Redness	Totals	
				Involvement	Swelling or Redness or Both
Right shoulder	30	2		32	2
Left shoulder	30	4		34	4
Right elbow	35	8	1	44	9
Left elbow	34	8	2	44	10
Right wrist	32	13	1	46	14
Left wrist	30	11	1	42	12
Right fingers	19	8	5	32	13
Left fingers	20	9	4	33	13
Right hip	15			15	
Left hip	16	1		17	1
Right knee	31	11	1	43	12
Left knee	26	13		39	13
Right ankle	21	8	2	31	10
Left ankle	21	6	2	29	8
Right foot (including toes)	14	3		17	3
Left foot (including toes)	14	3		17	3
Vertebrae of the neck	9	0		9	
Vertebrae of the back	4			4	
Clavicles		1		1	1
Pubes		1		1	1

The wrists and elbows were the joints most frequently involved with the knees, shoulders, fingers and ankles following in order. The following tabulation shows the number of joints involved in each patient.

Joints Involved	Patients	Joints Involved	Patients
1	8	9	1
2	5	10	4
3	6	11	3
4	3	12	5
5	4	13	4
6	6	14	4
7	6	15	2
8	5	16	2

The 15 patients with generalized pain in the arms and legs are not included in the preceding list.

The shortest duration of involvement of the joints was two days, the longest several months. The involvement subsided within one week in 10 patients, within from one to two weeks in 12, and within from two to four weeks in 12. In 34 the joints were still involved at the end of a month and in 3 at the end of five months. In the 34 cases were included those in which some definite pain or pain and swelling showed in any joint which had been involved from the onset. In the period of from one to five months the pain and swelling in most of the 34 cases subsided.

Paracentesis of two joints with fluid revealed yellow cloudy fluid in which on standing a slight flocculent precipitate appeared. Microscopic examination revealed polymorphonuclear leukocytes. Cultures taken from the fluids showed a pure culture of *Haverhillia multiformis*.



Fig 7—Photograph showing swelling of the joint of the left knee



Fig 8—Photograph showing swelling of the joint of the left knee

Respiratory Involvement—Sore throat appeared in 39 cases, or a little less than one half. It appeared at any time from the first to the twenty-fifth day of the disease, and at the eighth or ninth day on the average. It came on most frequently during the stage of relapse. The duration was from one to twenty-five days, averaging six and a half days. The soreness was slight, dysphagia being present in only 3 cases.

The throat showed a diffuse dull redness with capillary injection extending over the soft palate. Cultures showed the organisms usually found in the throat. The tongue was slightly coated.

Cough occurred in 21 cases, and was more or less dry and non-productive and not severe. It occurred with the slight sore throats. Two patients, aged 3, had croupy coughs during the onset of disease. Three patients complained of pain over the larynx with slight hoarseness, and slight tenderness on pressure over the larynx was present during the latter stage of the disease. One of these suffered loss of voice. Hoarseness in another lasted two weeks.

Bronchopneumonia developed in 2 cases on the third and fifth day of the disease and lasted about one week. One of the patients was markedly delirious, attempting to throw himself out of the window and requiring restraint. The physical signs were definite in both cases. Acute bronchitis occurred in 3 others, with cough and the raising of sputum without definite signs of pneumonia.

Organic Findings—Apparently the heart was not affected by the disease. No cardiac enlargement was present. In only 4 patients were murmurs found, 3 caused by functional disorder and in the other due to an old arrested endocarditis with no signs of an acute flare-up. The pulse rate was relatively low.

The edge of the liver was palpable in 1 case, but was not tender, and no jaundice was present.

The edge of the spleen was palpable in 7 cases, but this was thought to be a coincidence.

Abdominal pain and distention were present in the 2 patients with pneumonia, while abdominal pain alone was found in several others during the onset, with vomiting, but lasted only a day.

The genito-urinary tract showed no symptoms and appeared free from the infection. One patient showed frequency which was thought to be a reflex action to the pain and swelling of the symphysis pubis, which was involved in the disease. This patient had normal urine. Urinalysis in 14 cases gave essentially negative results.

There was no enlargement of lymph nodes.

Blood—The blood was examined in 23 patients from the first day to the fourth week of the disease. The composite picture of the white cell elements was 11,500 white blood cells per cubic millimeter, 70 per cent polymorphonuclears, 21 per cent lymphocytes, 6 per cent large monocytes, 2 per cent eosinophils, and 1 per cent basophils.

At the onset and throughout the disease the number of cells was just as often above the mean as below. The same can be said of the differential count. The white blood cell count varied from 5,680 to 18,888 (in a girl of 8 months). The polymorphonuclear count varied from 62 to 86 per cent. In babies and children the lymphocyte count

was higher, varying from 9 to 32 per cent. The large mononuclears varied from 4 to 11 per cent, the eosinophils from none to 6 per cent and the basophils from none to 2 per cent.

The red blood cell count varied from 3,728,000 to 4,456,000, the average being about 4,000,000. The hemoglobin ranged from 65 per cent, in a girl of 12 in the third week of the disease, to 95 per cent in a man in about the same stage of the disease. The average hemoglobin value was 80 per cent. The red cells showed some achromia, and the platelets in smears were normal.

TABLE 2—*Blood Cultures of 17 Patients*

Patient	Date of Onset	Date of Culture	Day of Disease	Haverhillia Multiformis
A A	Jan 21	Jan 29	9	+
		Feb 18	29	—
B E	Jan 20	Jan 23	4	+
		Feb 23	35	—
B L	Jan 21	Feb 6	17	+
K J	Jan 13	Jan 23	11	+
		Feb 6	25	+
K M	Jan 29	Jan 29	1	+
		Feb 6	9	—
P R	Jan 21	Jan 25	5	+
		Jan 28	8	+
		Feb 10	21	—
H W	Jan 19	Feb 10	23	—
L M	Jan 24	Jan 24	1	— (Contaminated)
L E	Jan 20	Jan 24	5	—
L A	Jan 17	Feb 20	35	Overheated
S J	Jan 15	Feb 6	23	+
R A	Jan 23	Jan 24	2	+
		Feb 20	29	Overheated
P L	Jan 18	Feb 6	20	—
W S	Jan 20	Jan 24	5	+
C G	Jan 21	Feb 19	30	— (Contaminated)
G M	Jan 21	Feb 1	12	—
A L	Jan 22	Feb 1	11	— (Contaminated)

The blood pressures were essentially normal.

Blood cultures were taken in 17 cases, with the results shown in table 2.

The blood cultures were positive in 11 of 17 cases. There were positive cultures on the first day of the disease and in 1 case as late as the twenty-fifth day. The earliest negative culture was obtained on the ninth day of the disease. The earliest positive culture that was followed by a negative one later was from blood which yielded a growth of the organism on the first day of the disease and which gave no growth on the ninth. Repeated blood cultures were done only in 6 cases. Dark-field illumination of the blood in 2 cases showed no *Haverhillia multiformis*.

Involved Joints—Cultures from taps of the joints on the ninth to eleventh days of the disease in 2 patients were positive. At this time both joints showed floating patellae. The cultures were not repeated.

Roentgen examination of an infected joint on the twenty-first day of the disease revealed the following. The left knee showed marked swelling of the soft tissue. The patella was pushed forward from the femur. The posterior part of the cartilage on the upper articular surface of the tibia had a fuzzy indistinct appearance. There was also a moth-eaten appearance of the border of the external condyle of the left femur.

Roentgen examination repeated on the thirty-third day of the disease revealed a degree of destruction over the external condyle of the left knee, which seems to have increased since the previous reading. Roentgen examination of a joint of another patient on the thirty-first day revealed a normal condition.

Spinal Fluid—A lumbar puncture performed on the nineteenth day of the disease showed 25 cc. of clear fluid with some microscopic blood.

Relapse—One case of the 86 showed a relapse.

Mrs. D., aged 33, on January 5 vomited four or five times, and had headache, backache and pain in the stomach. On January 6 she vomited four or five times. A rubellaform exanthem appeared over the extensor surfaces of the arms. On January 7, the arms were painful on motion and to the touch. She could not raise her hands to her face or shoulders. The rash was still present. On January 8 swelling appeared with fluctuation of the left elbow, the rash was gone. On January 9 the pain in the hands, wrists, shoulder and right elbow was gone. On January 12 there was no pain in the left elbow, and the patient was well. Nine days later there was a relapse. On January 21 she vomited twice and had pain in the elbows and knees. On January 22 she vomited once, and there was pain in the left elbow and stabbing pain in both elbows shooting down her arms to her wrists. An exanthem appeared on the extensor surfaces of the lower parts of the arms and legs and feet. On January 24 the right knee was swollen and tender.

Levaditi and his co-workers reported relapses on the sixth and tenth days of the disease, each relapse being ushered in with an elevation of temperature, an appearance of a second and third eruption similar to the first and increased pain in the joints. Blood cultures were positive on the first two exacerbations.

Complications and Sequelae—The complications were few. The pneumonia and bronchitis that accompanied the disease in some cases can be classified as such, but have been described under "Respiratory Involvement." In one case, two days before the pneumonia appeared, a positive blood culture was obtained. Whether the pneumonia was due to *Haverhillia multiformis* or to a secondary invader was not determined as no puncture of the lung was done. The pneumonia was bronchial. One case showed involvement of the middle ear with no specific organ-

ism discovered. Toward the end of the course in 1 patient a typical streptococcic sore throat with membrane developed. The other mild sore throats are described under "Respiratory Involvement."

The skin over the extremities showed desquamation, and in 2 cases blebs appeared around the ankles. The organisms found were gram-positive diplococci and diphtheroids.

Of the patients in whom arthritis persisted for over five months, 2 still had recurring pain and swelling in the previously involved joints, associated with inclement weather, in September 1928. No changes in bone or cartilage were noted. One of the patients seen in September 1928 stated that he used crutches for seven months. Examination revealed a normal joint, but he stated that five days previously with the onset of rainy weather, the joint became swollen and painful. The discomfort lasted for three days, clearing with the weather. A second patient reported similar trouble with his joints. He is at present in a hospital for patients with tuberculosis. A third patient had moved away from the vicinity, and was not traced. Whether the etiologic agent still persists in these joints is doubtful. It is known that the blood of 2 of these patients was normal the last time blood cultures were made. It is possible that secondary causes are maintaining the arthritis.

PATHOLOGY

Essentially nothing is known about the pathologic processes, since in both epidemics there were no deaths and biopsy specimens were not made.

BACTERIOLOGY

Parker and Hudson² found in cultures from the blood and from the fluid of involved joints an organism, *Haverhillia multiformis*, of variable form, appearing chiefly as rods from 2 to 15 μ m long and from 0.2 to 0.5 μ m wide, sometimes paired, often as filaments or threads with true branching. A marked characteristic is the occurrence of a swelling or a knob at any point in the rod, from four to five times the diameter of the rod. This does not take the spore stain. The organism does not stain well with ordinary aniline dyes, is gram-negative and nonacid-fast.

Haverhillia grows best at atmospheric oxygen pressure or under a partially anaerobic condition in ascitic fluid broth or on solid medium composed of equal parts of glycerin extract of potato and infusion broth to which egg yolk is added.

The organism was most virulent for white mice, which it killed in from sixteen to forty-eight hours after intraperitoneal injection. Mice could be immunized by sublethal doses of living cultures or by dead cultures against fatal doses for control mice, this immunity persisting

for at least two months. The serum of immunized rabbits showed precipitins and agglutinins for the organism in dilutions up to 1:5,000, against all strains. The absorption of antibodies by one strain was complete.

IMMUNITY

Little evidence is available for conclusions as to natural or acquired immunity.

There were 231 persons in the families, in which the disease was recognized in 86 (37 per cent). A considerable number of these, however, partook of milk rarely or not at all. Fifty-one insisted that they took no milk during January, and the majority gave a history of small and infrequent partaking.

Eleven families received milk directly from the dairy. Of these, all but 1 had the disease, the exception being a family in which boiling the milk was practiced. Twenty-six infected families received the same supply through stores, but a reliable record of all who obtained the milk from the stores could not be obtained. Four persons became residents of infected households during the epidemic. The disease developed in 2 of these, and the other 2 took no milk.

The study of agglutinins in the blood of patients after recovery and in that of the uninvolved members of the families was not undertaken, as continued cooperation in getting specimens of blood, after the serious upsets the patients had gone through and with the complete removal of further danger, could not be secured.

Eighteen patients were tested intradermally with a killed culture of the organism on May 27, 1926, from one hundred and twenty-four to one hundred and forty-two days after the onset. Fifteen showed reactions from 1 to 3 cm. in diameter. Control tests with the medium were negative. Control tests on 10 persons who had not had the disease or taken the contaminated milk were negative. No tests were made in persons in the infected families who escaped the disease.

DIAGNOSIS

In epidemics it is doubtful if any difficulty in diagnosis would occur, even if blood cultures were not taken. The picture is characterized by (1) abrupt onset with chills, fever, malaise, vomiting and headache, (2) an early eruption, rubellaform or morbilliform, occurring first, and often only, on the extremities especially about the ankles and wrists and tending to become hemorrhagic, (3) a multiple arthritis of varying, but often of a severe and crippling, degree, and (4) a fever curve of abrupt rise with remission in from two to five days, and after a few days of relative freedom from symptoms a recurrence with which the arthritic manifestations appear. In isolated cases, especially if

atypical, probably great clinical difficulties might occur. The frequent association of eruptions with manifestations in the joints in a number of distinct as well as obscure conditions makes the demonstration of the organism by blood culture or puncture of the joints essential to recognition.

Differential Diagnosis—The common contagious eruptive diseases, as measles, rubella and scarlet fever, may readily be differentiated by the clinical pictures.

Rheumatic arthritis offers no difficulty, since the peculiar remittent (saddleback) fever of epidemic arthritic erythema has no counterpart in rheumatic fever. There is no tendency to cardiac involvement, and although manifestations in the throat are common, they tend to a diffuse catarrhal type of injection without exudate or tendency to involve the lymphoid tissue.

There are many points of similarity with dengue. The cause of the Chester epidemic was generally considered to be dengue. The abrupt onset with chills, fever, headache, malaise and generalized pains, the remission of fever after three or four days with a recurrence after two or three days of normal temperature, and the morbilliform rash on hands and feet, forearms and lower part of the legs are common to both. Postorbital tenderness or pain on moving the eyeballs is not evidenced in Haverhill fever. There is no tendency to suffusion of the eyes or congestion of the face and no leukopenia with an increased percentage of lymphocytes. Hematemesis and jaundice are practically absent. The pulse rate is not especially low. Moreover, there is definite arthritis in most cases of Haverhill fever, although in many, objective signs may be slight and rarely absent. The rash, while similar, does not tend so commonly to involve the trunk extensively, and usually appears in the first febrile period instead of with the recurring fever as in dengue. The duration of the secondary fever and the arthritic symptoms is much more prolonged than in dengue and almost always lasts more than the two or three days noted in dengue.

Blood cultures would serve for positive differentiation of Haverhill fever.

During epidemics the epidemiology would serve, dengue being spread only by mosquitoes of the species *Aedes aegypti* (*Stegomyia calopus*), while Haverhill fever is spread only (?) by food.

Erythema infectiosum (Escheich), although accompanied by pain in the joints, differs in that the eruption appears on the sides of the face and is absent from the palms and soles, as well as by the development of larger circinate and serpiginous and coalescent lesions. The duration of Haverhill fever is usually much greater than the fever in infectious erythema (from five to ten days). Febrile reactions such as occurred in many of our cases are unknown in infectious erythema.

The eruption in erythema multiforme may at times simulate that seen in Haverhill fever. However, the larger, coalescent areas and the circinate, serpiginous and gyrate forms so characteristic of multiforme erythema were never seen in the cases of Haverhill fever. Involvement in the joints in erythema multiforme is certainly less likely to show definite swelling or to be so persistent as that in epidemic arthritic erythema. It is probable that some of the conditions classed in the large and somewhat obscure group of multiforme erythema, as shown by the report of Levaditi, Nicolau and Poincloux, are really identical with Haverhill fever.

Erythema subitum may be excluded by the appearance of the eruption in Haverhill fever frequently before the defervescence of the initial fever, the recurrence of fever, the arthritis and the absence of mononucleosis.

Influenza was a common diagnosis at the onset. The absence of cough and the widespread catarrhal signs of influenza, the appearance of the eruption, the recurrent fever with arthritis and the absence of leukopenia distinguish Haverhill fever.

Malta fever gives rise to some confusion, especially the form due to *Brucella abortus*. Both diseases are spread by contaminated milk and are characterized by tenderness and swelling of the joints, as well as by somewhat similar relapsing fevers. The more abrupt onset in Haverhill fever, the shorter initial fever as well as the relatively much shorter secondary fever would probably differentiate them. The involvement in the joints in Haverhill fever is often persistent, and while multiple does not tend to "skip about." There is no characteristic leukopenia with relative lymphocytosis and no splenomegaly. Neuritis and orchitis, so common in Malta fever, are absent in Haverhill fever. Blood cultures, agglutination tests with *Brucella melitensis*, *B. abortus* and *B. parameitensis* and Burnet's intradermal test would certainly settle any doubt.

Rat-bite fever has an interesting but obscure relationship to Haverhill fever. It is probable that rat-bite fever is due to *Spirochaeta morsus-muris* (Futaki,¹⁶ Kaneko and Okuda,¹⁷ etc.), which has been found in the local lesions and the blood. Mooser¹⁸ found this organism in the blood of a wild rat, *Mus decumanus*, and in the conjunctiva of rats and guinea-pigs experimentally inoculated through bites of ani-

16 Futaki, K., Takaki, I., Tamguchi, T., and Osumi, S. *Spirochaeta Morsus Muris*, N. S. P., the Cause of Rat-Bite Fever, *J. Exper. Med.* **25** 33, 1917.

17 Kaneko, R., and Okuda, K. Contribution to the Etiology and Pathology of Rat-Bite Fever, *J. Exper. Med.* **26** 363, 1917.

18 Mooser, H. Spiral Organism Found in Wild Rat, *J. Exper. Med.* **39** 589, 1924.

mals suffering from the conjunctival and corneal infection. Whether the cases from which *Streptothrix muris-ratti* was isolated (Schottmueller,⁸ Blake,⁹ Tunnichiff¹¹) represented a different variety of infection or were simply complicated by this organism remains uncertain. Strangeways¹⁴ recently showed that *Streptobacillus moniliformis* is frequently present in the nasopharynx of laboratory rats and wild rats but not in the blood.

The reported cases of rat-bite fever in which *Streptothrix muris-ratti* has been found do not differ essentially from those showing *Spirochaeta morsus-muris*. The chief characteristics are a variable incubation of from one or two days to eight weeks (Crohn¹⁰), but usually over two weeks, local cellulitis, lymphangitis and lymphadenitis, leukocytosis, an eruption, usually general but at times only in the region of the local inflammation and often from 2 to 3 cm in diameter, more commonly appearing with the recurrent fever, chilliness, headache, pains in the muscles, tenderness of the nerve trunks, and a strikingly recurrent fever. The febrile period usually lasts from three to five days, may be single but usually recurs from three to ten times and occasionally many more over a period of days, weeks or months. The symptoms abate during the afebrile periods and show exacerbations, including the eruption, with the recurrent fever. No arthritis has been reported.

How much difference entry of the infection through a wound would make is not now evident, but Haverhill fever differs from rat-bite fever in the following characteristics: the incubation period is short (so far as known), leukocytosis is slight or absent, multiple recurrences of fever comparable to those in typical rat-bite fever are not found, the rash is smaller and more uniform in size, occurs especially on the extremities and does not recur with the return of fever, and the involvement of the joints is one of the characteristic features. Of course, no local inflammation with lymphatic involvement is present. The mortality of Haverhill fever is nil to date as compared with about 10 per cent for rat-bite fever. In Levaditi's case the eruption recurred with each febrile outbreak.⁵

PROGNOSIS

The prognosis is good. In the two epidemics of about 500 cases no deaths occurred. As to permanent crippling owing to involvement of the joints, it is difficult to say. Certainly few patients are left with residual effects. At the end of two and a half years only 3 of the 86 patients had symptoms: men, 54, 45 and 44 years of age. The first of these showed some contractures of the muscles of the thigh, although

19 Crohn, B. B. Rat-Bite Fever, *Arch. Int. Med.* **15** 1014 (June) 1915

the swelling in the knee had subsided entirely. On the eighty-fifth day of illness the x-ray picture showed a considerable degree of atrophy of bones and narrowing of the articular space—but no other positive change about the joint. An earlier report on the thirty-third day of the disease stated that there was a degree of destruction over the external condyle of the femur. The patient was discharged from bed. At his age, although all other joints have cleared, there appears to be little chance of his ever being fully well again. Of the other 2 men, 1 recently examined during the absence of swelling or pain showed no deformity or limitation of motion of any of the joints.

The arthritis of the children and young adults has all cleared. It can be concluded that early age favors the prognosis, for only 29 per cent of the patients under the age of 21 showed involvement of the joints at the end of eight weeks in comparison with 58 per cent of those over 21, a ratio of 1:2. Whether the joints that have been infected and healed are more susceptible to further involvement in later life is to be determined through the passing of time.

PROPHYLAXIS AND TREATMENT

Pasteurization of milk supplies should be required. Whether the disease can be spread by other means is not known, but other raw foods obviously might be factors. No contagion was evident.

No specific treatment was found. The patients had been treated expectantly with salicylates in various forms and hypnotics. Narcotics were freely used.

Our observations were begun three weeks after the outbreak of the disease when relatively few cases were available for therapeutic study. Sodium salicylate, acetylsalicylic acid and strontium were administered to the point of toxicity without relief. Quinine and the iodides also gave no definite result. To 1 patient still acutely sick in the third week 0.59 Gm. of neoarsphenamine was given intravenously. The temperature dropped to 96 F., but rose in four hours to 100 F. The patient was slightly better the next day. There was no change in the arthritis, which persisted in his case for months. One patient in the fourth week received 5 cc. of a 1 per cent mercuriochrome solution intravenously, an hour later there occurred a severe chill lasting for thirty-five minutes followed by vomiting. The temperature rose to 104.2 F., to return within four hours to the previous level. There was no improvement in the condition in the joints or in the temperature curve.

Immobilization of the infected joints was usually done with supports and pillows. Splints were not usually used partly owing to the limitations of work in the field.

Decubitus had to be carefully guarded against. Diathermy and radiation treatments were used in some of the hospital cases by Dr McFee with some symptomatic relief but little apparent effect on the course of the arthritis. Some contracture developed in the worst case, but great difficulty was found in managing the patient. The usual treatment of rest, high intake of fluid, oral hygiene, simple antiseptic sprays for the throat and occasionally oily sprays was followed.

SUMMARY

An epidemic of a disease, apparently a new clinical entity, named epidemic arthritic erythema or Haverhill fever is described. It is characterized by an abrupt onset, often with a chill, a rubellaform to morbilliform eruption, often scanty, chiefly on the extremities, with a tendency toward hemorrhage into the lesions, and an inflammation of the joints with marked pain and tenderness not infrequently of prolonged duration.

The disease occurred as a markedly localized epidemic and was undoubtedly spread through the raw milk supply.

An organism, described only once before, is believed to be the cause, having been found in the blood stream in 11 of the 17 cases in which the blood was cultured and in the fluid of the joint in the 2 cases in which the fluid was cultured.

Agglutinins were present in the blood of the infected persons but absent in the controls.

Cutaneous reactions to killed suspensions were present in 83 per cent of the patients tested late in convalescence, although absent in the controls.

Although crippling may be marked for a time, recovery tends to occur in from one to two months, with a small number of patients having persistent joint symptoms. No fatalities occurred.

EFFECT OF THEOBROMINE ON PERIPHERAL VASCULAR DISEASE

CLINICAL OBSERVATIONS

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For a number of years the purine-base group of drugs has been widely used in the treatment of angina pectoris. The fact that the symptoms of this disorder can often be relieved for long periods of time by these drugs¹ seemed to indicate that they might be useful in the treatment of peripheral arterial disease.

Dock had noted that the pain of intermittent claudication was sometimes relieved by theobromine,² and in the reports of the Council on Pharmacy and Chemistry of the American Medical Association it is stated that claims for the occasional relief of pain by theobromine and theophylline preparations in angina and similar lancinating pains may be permitted.³

Diseases of the peripheral arteries also offered the opportunity of estimating to some extent, at least, objective evidence of improvement as well as subjective relief of symptoms. The objective criteria employed were the simple ones usually used in diagnosis and consisted of the appearance of the affected part, such as the change in color at a constant level and with a change in position, the presence or absence of swelling and the degree of integrity of the tissues. Other objective measures used were demonstration of the condition of the superficial vessels by palpation and inspection and the measurement of the surface temperature.

The last-mentioned criterion was thought to be fairly reliable and to furnish the opportunity for some quantitative estimation. For this purpose determinations of cutaneous temperature were made in all of the cases by means of a thermo-electric couple of the common type. The results of observation were then compared and correlated with the subjective symptoms.

From the Medical Services of St. Luke's and Cook County Hospitals.

1 Gilbert, N. C., and Kerr, J. A. Clinical Results in the Treatment of Angina Pectoris with the Purine-Base Diuretics, *J. A. M. A.* **92** 201 (Jan. 19) 1929.

2 Dock, W. The Use of Theobromine for Pain of Arteriosclerotic Origin, *California & West Med.* **25** 636 (Nov.) 1926.

3 Reports of the Council on Pharmacy and Chemistry. Therapeutic Claims for Theobromine and Theophylline Preparations, *J. A. M. A.* **94** 1306 (April 26) 1930.

Observations were made under uniform conditions of room temperature, posture of the patient and rest. The locations at which temperature readings were taken were always the same. Readings were recorded only after the patient had been in the room for a minimum period of one-half hour or until the temperature readings became constant. Air currents were eliminated as much as possible. No attempt was made to control humidity, but it is believed that the conditions for dispersion of heat were uniform.

The apparatus was demonstrated to be accurate to 0.1 degree C (0.18 degree F), but no attention was paid to changes of less than 0.5 degree C (0.9 degree F), which allows a reasonable limit for error.

Early in the course of this work several drugs were used, including caffeine, theophylline⁴ and others, but the best results seemed to be obtained with theobromine or theobromine sodium-acetate, and it is only the results with these preparations which are being reported.

The clinical material studied could be divided into three groups. These were arteriosclerosis with symptoms of intermittent claudication or with impairment of integrity of the tissues, thrombo-angitis obliterans, presenting the same symptomatology, and functional disturbances, including Raynaud's disease and acrocyanosis.

In the functional group, no improvement could be shown. In one typical case of Raynaud's disease, study of the effect of theobromine therapy over a period of six weeks showed no subjective improvement, and temperature readings showed a wide fluctuation from day to day. The only conclusion to be drawn was that theobromine was without effect in improving this condition.

Several cases of acrocyanosis were similarly studied. No improvement could be demonstrated. The red-blue color and puffy swelling of the hands in all of the cases were unchanged, and no rise in cutaneous temperature could be demonstrated even after prolonged administration of the drug.

In the groups of arterial diseases, the results were much more promising, but not all were successful. The following cases have been selected as typical.

REPORT OF CASES

CASE 1—A white woman, aged 74, entered St. Luke's Hospital complaining of constant severe pain in the right foot and toe, which was worse when the foot was dependent. It was impossible for her to walk. About a week before she had noticed swelling of the toe and a dusky red color, she thought that there was an infection about the nail. The pain continued and was often worse at night, sometimes assuming a cramplike character in the foot. During the previous winter she had noted difficulty in keeping her feet warm, the right one seemed

4 Also theophylline made soluble by ethylenediamine

particularly affected. She had previously been under observation in the cardiac clinic for arteriosclerotic disease of the heart and auricular fibrillation.

Examination showed a well marked general arteriosclerosis of the senile type in a frail, small elderly woman. The heart showed moderate enlargement and auricular fibrillation which was well compensated without digitalis at the time. The right foot was cold and bluish red, and the great toe dusky. There was a marked biphasic color reaction, with pallor on elevation. The toe showed puffy swelling, the nail was loose, and there was a seropurulent discharge from the nail bed. There were no arterial pulsations palpable in either foot. The right foot was much colder than the left. Roentgen examination of the feet showed marked calcification of the vessels of both feet.

This patient was under close observation in the hospital from May 21 to September 4, and then in the outpatient department until April 16, of the following year. Frequent cutaneous temperatures were recorded.

TABLE 1—*Arteriosclerosis with Ulceration of the First Toe of the Right Foot and Loss of the Nail (Case 1)**

Period of Observation	Average Temperature, C		Appearance and Symptoms
	Right	Left	
Control, 17 days	28.9	31.4	Color change marked, toe painful
Theobromine sodium acetate, 3 Gm daily for 21 days	31.29	33.19	Pain less severe, color better, toe improving
Theobromine sodium acetate discontinued for 15 days	30.2	32.6	Much better, toe nearly healed
Sodium acetate, 3 Gm daily for 12 days	30.2	32.4	No pain, able to walk
Theobromine (alkaloid), 1 Gm daily for 19 days	31.1	32.9	
Theobromine discontinued for 10 days	30.1	32.4	Foot in good condition, new nail grown, patient discharged taking 2 Gm of theobromine sodium acetate daily

* There was no medication other than that recorded except codeine for the relief of pain. The patient was confined to bed. Temperatures were taken on the dorsal surface of the feet proximal to the first toe.

During a control period of seventeen days the average temperature taken on the dorsal surface of the feet proximal to the first toe was 28.9 C (84 F) for the right and 31.4 C (88.5 F) for the left. During this time the foot looked bad, and the patient required sedatives for the relief of pain. Theobromine sodium-acetate was begun on June 7 (3 Gm daily divided into three doses and continued for twenty-one days). During this period the average temperature rose to right, 31.29 C (88.32 F), left, 33.4 (92.1 F). There was still pain, but it was less severe, and by June 23 the patient was comfortable, no sedative was necessary, and the color of the foot looked better. No other treatment was used except to protect the foot from pressure. During this period the maximum temperature was 32 C (89.6 F) for the affected foot, a rise of 3.1 degree C (5.6 degrees F) above the control average.

Theobromine was discontinued from July 2 to July 17, with the average temperature falling to right, 30.2 C (86.3 F) and, left, 32.6 C (90.6 F). Although the foot continued to improve, medication was continued again with a slight uniform rise and fall following its cessation. By July 29, the patient was able to walk and had no pain at night. The foot still showed change in color and loss of heat. By September 4, a new nail had grown, there was no discomfort, and

the patient was discharged taking theobromine sodium-acetate, 2 Gm daily, at intervals, with no gastric distress. In February of the next year, pain returned, and observations were renewed for three months. I was again able to show a corresponding rise in temperature and clinical improvement during theobromine therapy for a time, but later complete relief was impossible. Coronary thrombosis finally caused death.

As shown in table 1, sodium acetate was substituted for the theobromine salt for twelve days following a period of no medication. There was no rise in temperature during this period.

CASE 2—A white man, aged 59, said that he was able to walk slowly only about one-half block. He had a severe cramplike pain in the calf of the left leg, which forced him to stop for a few minutes, after which he was able to walk again. He had coronary thrombosis two years before and angina pectoris until recently, when precordial pain disappeared and auricular fibrillation set in. He had been having intermittent claudication for about three months. There was no impairment of integrity of the tissues, the dorsalis pedis and posterior tibial arteries

TABLE 2—*Arteriosclerosis with Intermittent Claudication (Case 2) **

Period of Observation	Average Temperature, C		Appearance and Symptoms
	Right	Left	
Control, 5 days	30.1	27.9	Able to walk less than 1 block without pain
Theobromine sodium acetate, 3 Gm daily for 7 days	31.8	30.9	No claudication walking about ward, discharged to outpatient department
Theobromine sodium acetate, 2 Gm daily for 14 days	31.6	30.9	Walked 4 blocks without pain, feet hot and burning at night
Theobromine sodium acetate, 2 Gm daily for 30 days			Some aching in the left leg, able to walk 3 blocks, feet warm at night

* Temperatures were taken on the plantar surface of the first toes. The room temperature was 25.5 C.

could not be palpated on the left foot but were good on the right. There was definite loss of heat. During a three day control period, cutaneous temperature taken over the base of the first toe showed an average for the left foot of 27.9 C (82.2 F) and for the right, 30.1 C (86.1 F). Theobromine sodium-acetate was given, 3 Gm daily, with a rise to a maximum temperature of 31.6 C (88.8 F) on the affected foot, which nearly equaled that on the other. The average for a period of eight days on this dose was 30.9 C (87.6 F), an average rise of nearly 3 degrees C (5.4 degrees F). At this time the patient was discharged from the hospital. He had no pain when walking about the ward and was able to walk four blocks without stopping. Because of gastric distress the dose was reduced to 2 Gm daily, and observations were continued at weekly intervals. The increase in temperature was fairly well maintained until the patient discharged himself. He was able to walk five or six blocks as rapidly as cardiac dyspnea allowed him to. During the period of maximum dosage he complained of a burning sensation at night in the feet and legs which has been a common complaint when rather large doses are being taken.

CASE 3—A woman, aged 60, with senile arteriosclerosis and varicose veins complained of pains in the legs, swelling, discoloration and tenderness. She could not sleep well at night because of the pain in the legs, which was more or less constant, and she was unable to walk because of weakness. She had been under

observation in the cardiac clinic for arteriosclerotic disease of the heart and auricular fibrillation. The feet showed marked varicosities, a dusky reddish-blue color, puffy swelling and pigmentation. Arterial pulsations could not be palpated. There was no impairment of the integrity of the tissues. Roentgenograms showed marked calcification of the vessels in the legs. There was definite loss of heat, about the same in both feet. During a twenty-five day period of observation no subjective improvement could be shown, nor was there an increase in surface temperature, which fluctuated within a moderate range.

CASE 4—F. H., aged 42, a white man with thrombo-angitis obliterans, complained of intermittent claudication. Left lumbar sympathectomy had been performed one year previously by Dr. Loyal Davis. Following lumbar sympathectomy the symptoms of Buerger's disease in the left leg and foot had disappeared, and he had been able to work without discomfort until about two months before, when he began to have pain in the calf of the right leg when walking. The foot became cold and showed a dusky discoloration. The patient was unable to walk more than two blocks without being required to rest, after which the cramplike

TABLE 3—*Arteriosclerosis and Varicose Veins (Case 3)**

Period of Observation	Average Temperature, C		Appearance and Symptoms
	Right	Left	
Control, 7 days	26.7	27.0	Feet cold and mottled, veins dilated, weakness and aching in legs during walking
Theobromine sodium acetate, 3 to 3.7 Gm daily for 11 days	24.6	24.5	No change in appearance or symptoms
Theobromine sodium acetate stopped for 5 days	25.0	25.1	No change
Theobromine sodium acetate, 2.7 Gm daily for 7 days	24.8	24.8	No subjective or objective change

* The patient was hospitalized and kept in bed for the first period of therapy. Temperatures taken on the plantar surface of the first toe remained constantly below the average room temperature of 25.5 C.

pain would stop and he could continue. Roentgenograms showed little evidence of arteriosclerosis. The left leg and foot were warm and dry, and perspiration was not evident. The color was pink and the circulation appeared to be good. The dorsalis pedis artery was faintly palpable. The right foot was cold and moist and showed a dusky, bluish-red color of the toe when the foot was dependent, which changed to white when the foot was elevated. There were no arterial pulsations to be detected below the popliteal artery. The patient was under observation for four months. During the initial control period the surface temperature averaged 28.6 C (83.4 F) on the dorsal surface proximal to first toe, that of the toe itself averaged 27 C (80.6 F). The readings over various areas on the left foot were about equal, with an average of 31.8 C (89.2 F) on the toe. The surface temperature on the dorsum of the foot after ten days during which theobromine sodium acetate was administered reached 32.6 C (90.68 F), the maximum for the period of administration, which covered thirty-three days, with the dosage varying from 2 to 3 Gm daily. During the first ten days the patient was able to walk five blocks, pain at night had nearly disappeared. The maximum distance he was able to walk was six blocks. With the higher dosage he also complained of a severe burning sensation in the affected leg at night. The sympathectomized leg showed a smaller increase in temperature, reaching a maximum of 1.7 degrees C (3 degrees F) above the average, and with an average increase for

the period of 0.6 degree C (1 degree F) With cessation of therapy there was a fall in temperature on the affected foot to approximately the control levels, but symptoms of intermittent claudication did not return to the previous degree of severity for thirty-four days, although the distance the patient could walk was gradually diminished

With restoration of therapy there was again a rise in temperature, and the patient was able to walk five blocks

CASE 5—Charles T, a white man, aged 53, with thrombo-angitis obliterans, entered St Luke's Hospital on March 1, 1930, with a history of pain in the right foot and toe for six months Pain was constant day and night, requiring sedatives daily and morphine at night The foot was badly discolored and cold, with beginning gangrene involving the first toe The arteries of the feet were not

TABLE 4—*Thrombo-Angitis Obliterans with Previous Left Lumbar Sympathectomy (Case 4)**

Period of Observation	Average Temperature, C		Appearance and Symptoms
	Right	Left	
Control period, 2 days	27.0	32.0	Intermittent claudication unable to walk 2 blocks at slow gait without pain, typical color reactions, arterial pulsations absent
Theobromine sodium acetate, 3 Gm daily for 36 days	29.6	32.8	Able to walk from 5 to 6 blocks slowly without pain even in cold wet weather complained of burning sensations in the legs, worse in the right
Theobromine sodium acetate discontinued for 34 days because of burning sensation at night	27.4	31.6	Comfortable for a time but at end of period pain returned, 2 blocks the limit when walking without stopping for rest
Theobromine sodium acetate, 3 Gm daily for 22 days	30.0	31.2	Improved as before, color better able to walk about 5 blocks, but not entirely without pain

* Temperatures were taken on the dorsal surface of the feet proximal to the first toe The room temperature was 25.5 C This patient complained of severe burning sensations in both legs during the periods of administration of theobromine The individual temperature readings showed more fluctuation than was usual, possibly because the patient was under observation during cold winter weather

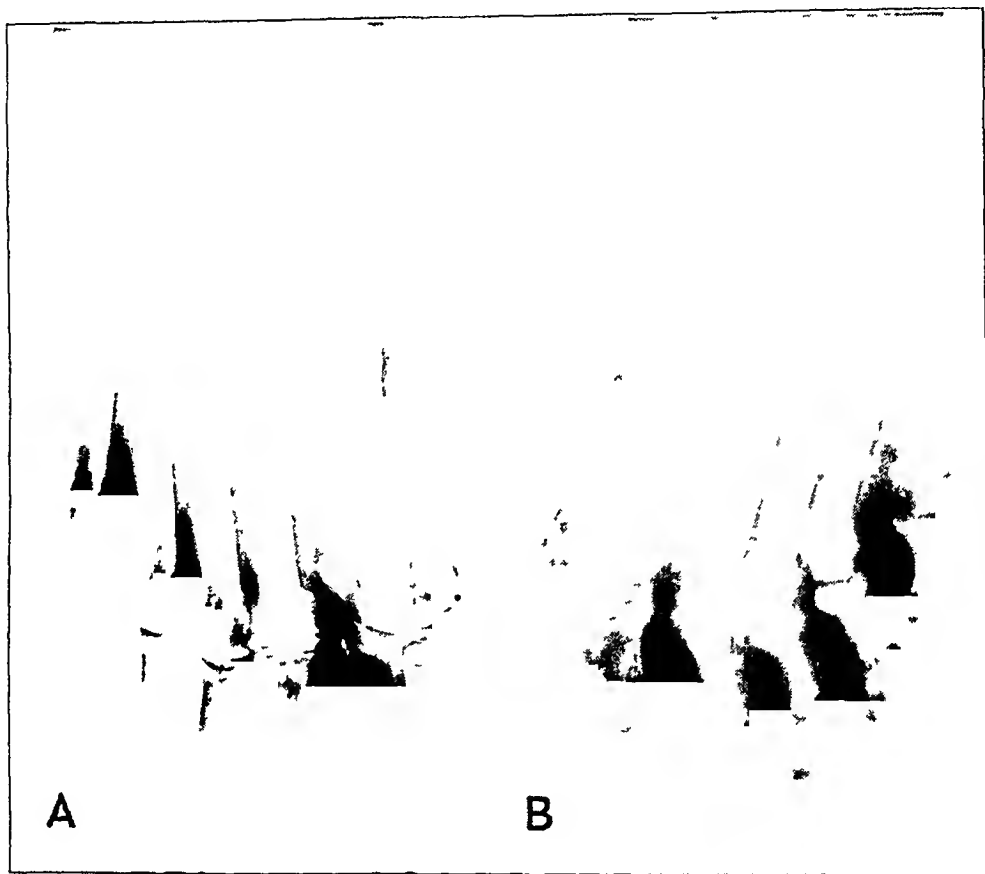
palpable, and roentgenograms showed no evidence of calcification The patient could not walk Theobromine sodium-acetate was without favorable response There was no subjective relief or a rise in surface temperature It was impossible to demonstrate vasodilatation by foreign protein fever or by spinal anesthesia It was therefore assumed that there was complete occlusion of the peripheral arteries of the foot

CASE 6—H A, aged 33, a white man with thrombo-angitis obliterans, entered Cook County Hospital complaining of pain in the right foot and great toe There were swelling and discoloration of the toes of the right foot, with beginning gangrene in the first toe The illness was of thirteen days' duration, following an alcoholic debauch Roentgenograms showed no calcification of the vessels The changes in color were well marked The arteries were not palpable It was impossible to maintain uniform room temperatures in this case, and the cutaneous temperatures showed less uniformity of response There was an initial rise from the control level of 29.8 C (85.6 F) on the affected side and 32.3 C (90.1 F) on the left to a maximum of 31.6 C and 33.2 C (91.7 F) respectively The average for the period of observation was 31.5 C (88.7 F) for the affected foot

and 32.8 C (91 F) for the other. There was no appreciable fall after theobromine was discontinued, during the period of observation. Relief from pain was prompt and complete. The foot improved remarkably in appearance, and a line of demarcation formed which was distal to what was expected before this therapy was instituted. The toes were amputated later, and the wounds healed, although slowly. The patient left the hospital without complaint of pain.

COMMENT

The material presented has been selected from a group of cases observed during the past five years. For many of these cases complete



Roentgen appearance of the vessels in case 1. In the left or unaffected foot (A) the artery appears to be completely calcified, while in the right foot (B) there is only patchy calcification. This foot was colder than the left and painful, and showed loss of integrity of tissue in the first toe.

data have not been recorded, but the clinical results of the use of theobromine and its salts in conjunction with other forms of treatment in arteriosclerotic disease of the peripheral arteries and thrombo-angitis obliterans have been sufficiently favorable to demonstrate its value.

It is particularly applicable to cases of arterial disease in the aged, in whom more energetic methods are impossible. As in case 1, a variable amount of relief may be provided over rather long periods of time, if there is sufficient capacity for dilatation of the affected vessels.

It is interesting to note that in this case roentgenograms demonstrated only a patchy calcification in the vessels of the affected foot, while in the other foot, which was symptom-free, the calcification was more nearly continuous (figure). It might be supposed that under such conditions a vessel the wall of which was completely calcified would be incapable of constriction or dilatation, while, on the other hand, a patchy sclerosis might result in increased irritability and consequently angiospasm with ischemia to the tissue supplied. It is in cases of this type that benefit from theobromine may be expected.

In thrombo-angitis obliterans a similar set of conditions may exist. In early cases in which occlusion is not too extensive and in which there is a large element of angiospasm, theobromine given in sufficient amounts has been successful in bringing symptomatic relief as well as restoration of minor degrees of impairment of tissues. This has been observed particularly in instances of involvement of the upper extremities. Case 5 clearly shows that when organic impairment of the larger vessels is extensive, no objective or subjective improvement occurs. In this case it was impossible to demonstrate an element of angiospasm. The failure in case 3 can be explained on a like basis.

It is, however, unfortunately true that many patients in whom a good response was expected failed to improve. This has been particularly true in cases of diabetic arteriosclerosis and gangrene. In none of these cases has it been evident that theobromine was responsible for improvement that could not be accounted for by proper control of the diabetes and the complicating infection.

The mode and location of the action of these drugs can only be surmised. The fact that they are without effect in purely functional disorders, as in Raynaud's disease, and are most active in disease of the medium-sized and smaller arteries, where an element of angiospasm may exist, suggests that the effect may be a local one, possibly that of reducing the increased irritability of the musculature of the diseased vessel wall. This interpretation is in agreement with the views of Sollmann and Pilcher, who stated that caffeine is a vasodilator acting by peripheral inhibition of vasoconstriction.⁵ It is likewise interesting to note that the coronary arteries are of the same class of vessels.

CONCLUSIONS

1 Theobromine and its salts, particularly theobromine sodium-acetate, act as peripheral vasodilators.

2 They are useful in the treatment of peripheral arteriosclerosis and early cases of thrombo-angitis obliterans in which there is a large ele-

⁵ Sollmann, T., and Pilcher, J. D. The Actions of Caffeine on the Mammalian Circulation, *J. Pharmacol. & Exper. Therap.* **3** 19, 1911.

ment of angiospasm Their use results in subjective improvement in intermittent claudication, and repair of loss of tissue integrity has been noted

3 They are not effective in all cases, but the results obtained with them are sufficiently good to make them a valuable adjunct in the treatment of peripheral vascular diseases

CHANGES IN THE CENTRAL NERVOUS SYSTEM RESULTING FROM CONVULSIONS DUE TO HYPERINSULINISM

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A series of experiments with animals was designed to investigate whether or not repeated convulsions for varying periods of time, induced artificially by the production of hyperinsulinism, would lead to organic lesions in the brain. Convulsions are generally classified as organic when there are associated with them demonstrable intracranial pathologic conditions, and as functional when no such evidence exists.

It is still a question whether convulsions per se lead to definite organic cerebral lesions. Spielmeyer¹ showed that focal anatomic lesions of the necrobiotic type in the brain can result from a purely functional circulatory disturbance. Furthermore, he noted similar lesions associated with convulsions in a variety of intoxications, such as eclampsia of pregnancy, pseudo-uremia, carbon monoxide intoxication, chloroform narcosis and infections, in none of which there was any organic occlusion of a cerebral vessel. All of these he regarded as due to vasomotor disturbances.

Foster Kennedy, in a discussion of Spielmeyer's paper,^{1b} described the occurrence of marked cerebral ischemia during an epileptic fit. This clinical observation was made by him on a patient whose brain was exposed during an operation under local anesthesia.

The importance of this subject, and the meagerness of knowledge concerning the effects on the central nervous system of convulsions of varying intensity, duration and frequency, led us to undertake this study.

PROCEDURE

Fourteen rabbits, weighing from 2 to 5 pounds (0.9 to 2.3 Kg), were employed in this study and were fed the regular stock diet. Convulsions were produced by the intravenous injection of insulin into animals which had previously fasted for eighteen hours. The dosage of insulin required to produce an attack varied considerably (from 2 to 12 units) for different rabbits. In certain instances it was found necessary during the course of the experiment to increase the dose to bring about an attack. The convulsions, as a rule, set in from two to six hours after injection of the insulin. The animals were allowed to remain in convulsions for

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1 Spielmeyer, W. (a) *J Ment Sc* **76** 641, 1930, (b) *J Nerv & Ment Dis* **71** 293, 1930, (c) *Anatomic Substratum of Convulsive State*, *Arch Neurol & Psychiat* **23** 869 (May) 1930.

periods ranging from three minutes to several hours. The convulsions were then terminated by the intravenous administration of 10 cc of 50 per cent dextrose. Two or three days were allowed to elapse between successive injections of insulin into the same animal. Whenever possible the experiment was conducted over a period of about three months. At the close of the experiments the animals were killed with ether, and autopsy was performed within two hours. Blocks of tissue for histologic examination were taken from the medulla, pons, cerebellum, basal ganglions and frontal, parietal and temporal lobes. They were fixed in 95 per cent alcohol and stained with toluidine blue by Nissl's method. The lesions were arbitrarily graded from — to + + + +, depending on the severity of the changes noted in the preparations.



Fig 1—A shrunken hyperchromatic ganglion cell showing a corkscrew process staining for a long distance. Nissl stain, $\times 750$.

RESULTS

Gross inspection of the brains at necropsy revealed no changes. Both hemispheres were symmetrical, the convolutions and sulci, respectively, were of the usual width and depth. There were no large or petechial hemorrhages and no edema. The microscopic pictures, which varied with the severity of the lesions, were graded from — to + + + + by the following criteria:

- No abnormal cells were found in any of the preparations.
- + Only occasional shrunken, hyperchromatic cells with corkscrew processes that stained for long distances were seen scattered among the nerve cells of the third and fifth cortical layers. Figure 1 is a photomicrograph of such a cell.

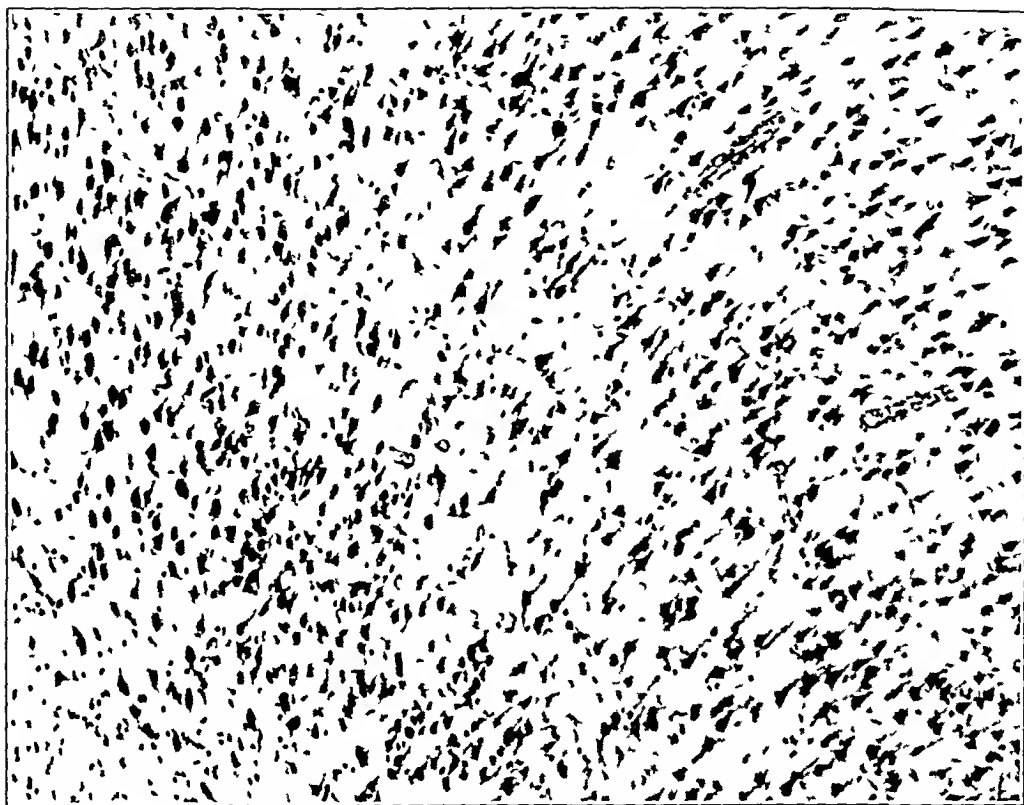


Fig 2—A zone showing many shrunken cells with corkscrew processes Nissl stain, $\times 125$

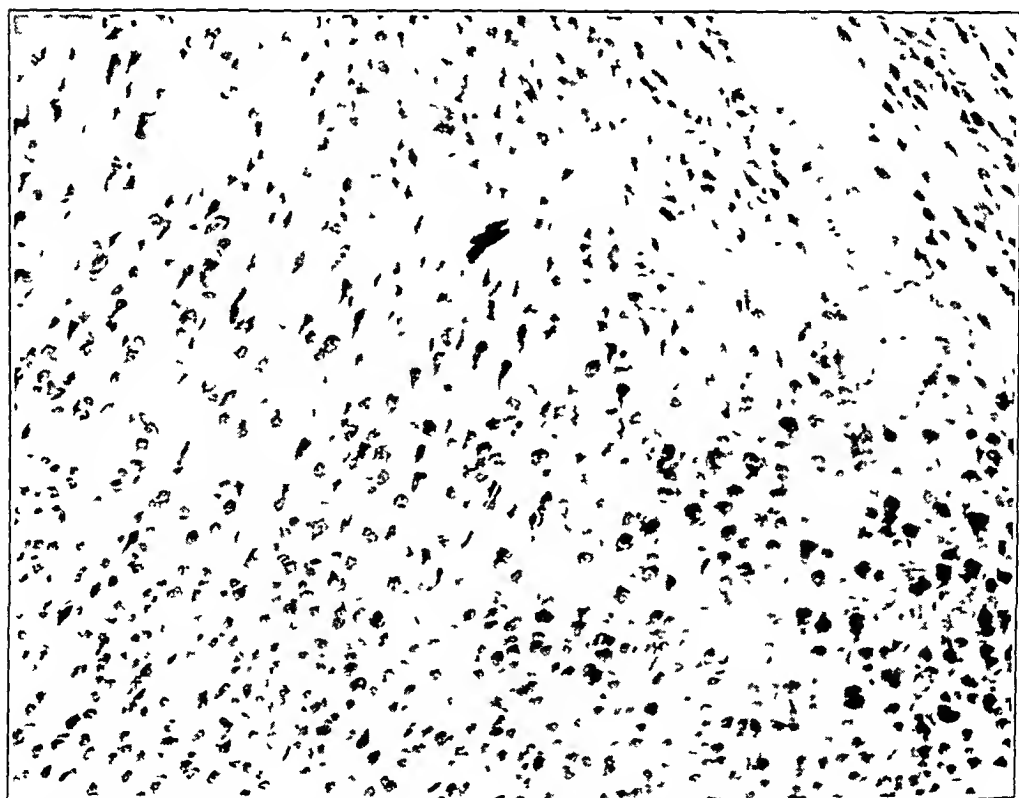


Fig 3—A zone of necrobiosis in which the cells stain poorly and faintly or are completely gone Nissl stain, $\times 125$

- + Definite but disseminated small zones showing these cells were found in the cerebral cortex
- ++ Many more such zones were present, and each contained many more shrunken, hyperchromatic cells. Figure 2 is a photomicrograph of such a zone
- +++ In addition to these zones, areas of necrobiosis were present in which many cells were completely absent or poorly stained. Figure 3 is a photomicrograph of such a zone
- ++++ The zones of necrobiosis were more extensive, and there was in addition a marked glial proliferation in these regions. Figure 4 is a photomicrograph of such a zone. Few nerve cells and many glia cells are seen in this figure, as contrasted with figure 5, which is from a comparable

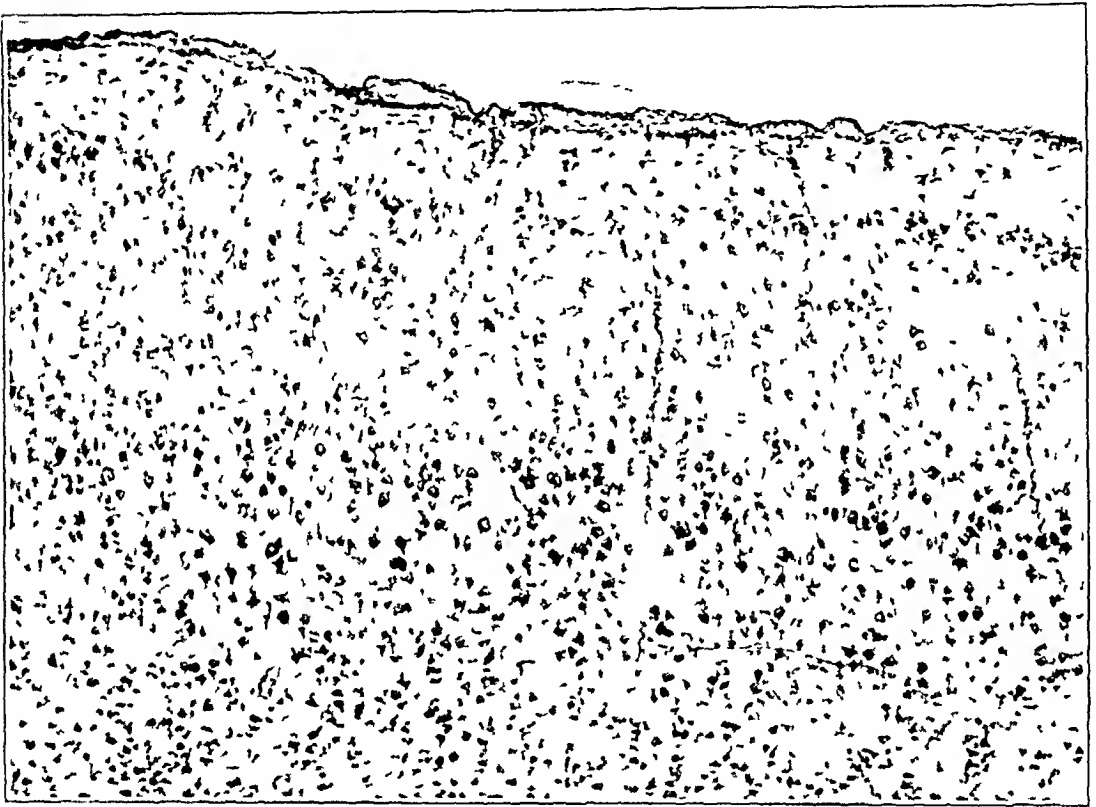


Fig 4—A zone of necrobiosis, showing more extensive lesion with marked glial proliferation. Nissl stain, $\times 75$

normal region under the same magnification from the opposite side of the same animal. Figure 6 shows more clearly under higher magnification the type of cells present in the necrobiotic area shown in figure 4.

The results of these experiments are shown in the table. Rabbit 4 received thirteen injections of $1\frac{1}{2}$ units of insulin, and at no time manifested either convulsions or tremors. On the twenty-second day encephalitis set in. The animal was killed and autopsy was performed the same evening. Examination of the brain showed only the lesions of encephalitis. Rabbit 3 received thirty-four injections of $2\frac{1}{2}$ units of insulin over a period of one hundred and four days and only once mani-

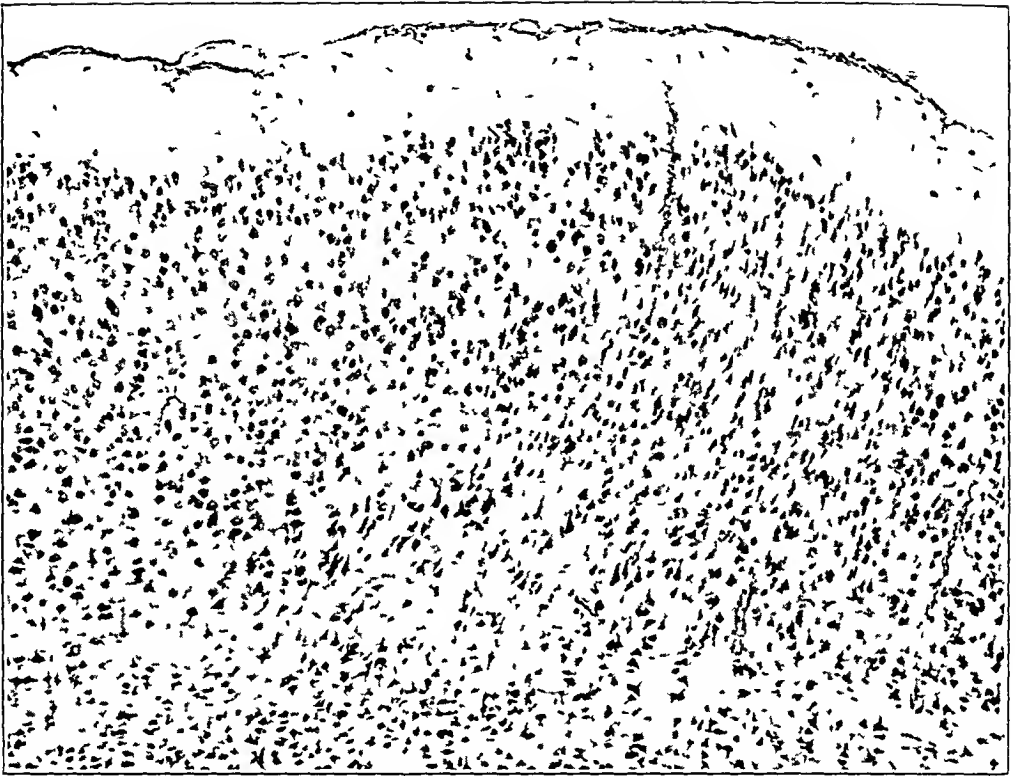


Fig 5—A normal area comparable to that in figure 4 from the opposite side of the same animal Nissl stain, $\times 75$

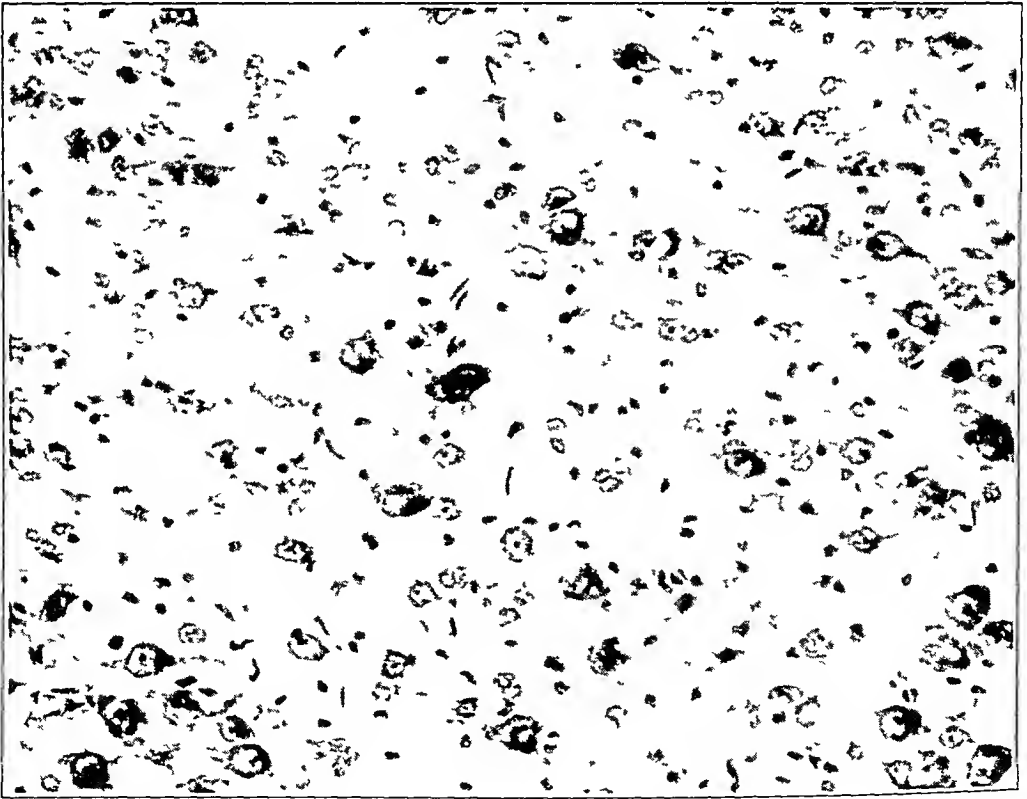


Fig 6—A portion of the zone in figure 4, showing the type of cells Many glia cells and a few nerve cells are seen Nissl stain, $\times 500$

fasted tremors for thirty minutes. There were no pathologic changes in the brain. Rabbits 5, 1 and 9 showed only minimal changes in the brain. Of these, rabbit 5, inoculated thirty-one times during the course of one hundred and five days, displayed two slight convulsions lasting three and thirty minutes, respectively. Rabbit 1 received four injections over a period of ten days and had two severe convulsions, during the last of which it suffered a fracture of the spine, with resulting paralysis of the hindlegs. Rabbit 9 was given twenty-one injections, and with the dosage employed (from 4 to 6 units) it was possible to

Insulin Dosage, Duration and Severity of Convulsion and Extent of Lesion

Rabbit	Weight, Lbs	Insulin, Units	No. of Injections	Convulsions			Comment	Duration of Experiment, Days	Microscopic Grading
				Slight	Severe	Duration			
4	2 $\frac{3}{8}$	1.5	13				Encephalitis set in	22	—
3	5	2.5	34	1		30 min		104	—
5	2	2	31	2		3 and 30 min		104	— +
1	2 $\frac{1}{4}$	2	4		2	4 hrs	Broke spine, paralysis of hindlegs	10	— +
9	4 $\frac{3}{4}$	4.6	21	11	1	15 min		77	— +
6	2 $\frac{3}{8}$	2	2		1	5 hrs	Broke spine, paralysis of hindlegs	6	+
8	4 $\frac{1}{4}$	3	1		1	4 hrs		1	++
2	3 $\frac{3}{8}$	2	8		7	6.3 min 1.4 hrs		20	++
7	3 $\frac{3}{8}$	3.5	25	8	12	9.3 min 3.20 min		105	+++
10	4	4.6	17	1	12	8.4 min 4.20 min		77	+++
11	3 $\frac{3}{4}$	4.6	19	3	9	5.4 min 4.20 min	Showed encephalitis histologically	76	+++
14	4 $\frac{1}{2}$	8	15		15	8.2 hrs 7.1 $\frac{1}{2}$ hrs		84	+++
13	4 $\frac{1}{2}$	8.10	18		14	14.2 hrs		85	++++
12	4 $\frac{1}{2}$	8.12	22	4	12	8.2 hrs 4.1 $\frac{1}{2}$ hrs		86	++++

produce only one severe convulsion lasting fifteen minutes. However, the animal did display tremors on eleven other occasions. The other rabbits (6, 8, 2, 7, 10, 11, 14, 13 and 12), all of whom had severe convulsions one or more times for variable periods of time, showed definite anatomic lesions, as seen in the table. Rabbit 14 showed many small foci of necrobiosis of the cortical ganglion cells and many more shrunken cells than did the preceding animals. It did not, however, show the extensive zones of necrobiosis and the glial proliferation in these regions seen in rabbits 13 and 12. Rabbit 12 showed marked glial proliferation in the extensive necrobiotic areas. Many shrunken cells were also found scattered throughout all the preparations of this animal. Rabbit 13 showed lesions similar to those formed in the preceding animal. In addi-

tion, however, it showed the exudative lesions of spontaneous encephalitis, although clinically it manifested no symptoms of this disease

The lesions of spontaneous encephalitis in rabbits cannot be confused with those found in these experiments. The former are of an exudative character, and consist of focal accumulations of small round cells, with some edema and necrosis. They do not cause the changes in the pyramidal cells noted here, nor are they characterized by necrobiotic changes.

COMMENT

It is quite apparent from these results that animals which have not had convulsions, or only slight ones on a few occasions, show either minimal or no cerebral changes, regardless of the number of injections of insulin they have received. However, even one convulsion, if prolonged and severe enough, may produce definite lesions in the central nervous system. Furthermore, the more prolonged or the more severe the convulsions, the more extensive are the lesions found, provided the animals are permitted to live long enough for the changes to develop. Popper and Jahoda² expressed the belief that insulin contains a component which directly affects the central nervous system so as to produce convulsions. They base this opinion on their own work and the work of others in which the convulsive effects of insulin were neutralized by the administration of caffeine, liquid petrolatum and other substances without in any way affecting the blood sugar. Others feel that the convulsions may be due to cerebral anemia. Several workers noted the fact that anoxemia of the brain, if prolonged and severe, is regularly followed by convulsions. Gildea and Cobb³ described lesions very similar to those seen in our experiments which they produced by ligating the carotid arteries of cats. What the exact mechanism is which produces the cerebral lesions in the rabbits cannot be stated definitely, but it seems to me that during the convulsions some circulatory disturbance takes place, with consequent anoxemia of the brain. During the more severe convulsions, these periods of anoxemia are sufficiently prolonged to cause the cerebral changes.

SUMMARY

- 1 Fourteen rabbits were employed in these experiments
- 2 Rabbits which did not have convulsions showed no lesions in the brain
- 3 Rabbits which had slight convulsions showed minimal or no changes in the brain

2 Popper, L., and Jahoda, S. *Klin Wchnschr* 9 1585, 1930

3 Gildea, E. F., and Cobb, S. *Effects of Anemia on Central Cortex of Cat*, *Arch Neurol & Psychiat* 23 876 (May) 1930

4 Rabbits which had severe convulsions one or more times showed definite anatomic lesions in the central nervous system

5 The greater the number and the more prolonged the convulsions, the more severe were the lesions

6 The milder lesions consisted of zones containing shrunken hyperchromatic cells with corkscrew processes The more severe lesions showed, in addition, zones of necrobiosis The cells particularly involved were the pyramidal cells of the third and fifth cortical layers

HEPATITIS AND CHOLECYSTITIS IN THE COURSE OF BRUCELLA INFECTION

REPORT OF A CASE

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Brucella infection in man is a relatively common disease in the United States, as shown by the increasing number of reports from all parts of the country. In the numerous clinical reports on the subject there is, however, relatively little to be found concerning the visceral manifestations of the disease in man. Clinically, in a few reported cases abdominal pain has been the predominant symptom and has led to the consideration of cholecystitis or appendicitis as the possible diagnosis. Simpson¹ has recorded twelve appendectomies and two cholecystectomies performed on patients with undulant fever. In two of the cases studied by Hardy and his associates² a diagnosis of cholecystitis was seriously considered. Leavell and Amoss³ reported a case of brucellosis in a patient whose illness was complicated by cholecystitis, and from whose bile they were able to isolate Brucella organisms. In their article they include the case reported by Bull and Gram in 1911. In addition, Amoss⁴ studied two other patients with brucellosis on whom cholecystectomies were performed.

The following case is recorded on account of its rarity, certain unusual features in the clinical picture and the relief afforded the patient by operation. The patient had an illness of several months' duration characterized by leukopenia and an undulating fever.

REPORT OF A CASE

History—W. O., an American, aged 57, married, an animal caretaker, was admitted to the University of California Hospital on Feb. 12, 1931, complaining of weakness, cough and fever. He had been well until three weeks before

From the Division of Medicine, Medical School, and Hooper Foundation, University of California.

1 Simpson, W. M., and Bowers, L. G. Surgical Aspects of Undulant Fever, *Am J Surg* 7: 597, 1929.

2 Hardy, A. V., Gordon, C. F., Borts, F. H., and Hardy, G. C. Undulant Fever with Special Reference to Study of Brucella Infection in Iowa, *Bull Nat Inst Health* no. 158, 1930.

3 Leavell, H. R., and Amoss, H. L. Brucella Infection. Case Report, Cultivation of Brucella from Bile, *Am J M Sc* 181: 96, 1931.

4 Amoss, H. L. Localization of Brucella, *Internat Clin* 4: 93, 1931.

admission, when he was seized with a severe sharp pain in the right side of the chest, accompanied by a "shaking" chill, headache, cough and a temperature of 104 F. His family physician the following day made a tentative diagnosis of bronchopneumonia. Five days after the onset of his illness the patient became irrational, restless, talkative and delirious. For six days he had several severe chills daily and a temperature in the afternoons of 40 C (104 F). There was no appreciable change in his condition after he had been in bed three weeks. He remained semicomatose and became incontinent of urine and feces. When the patient failed to improve, he was referred to the hospital.

The past history was unimportant except that he had had typhoid fever when 20 years of age. He had lived in California for the past thirty-seven years as an animal caretaker in an experimental laboratory where he came indirectly in contact with animals that had been experimentally infected with *Brucella abortus* and *Brucella melitensis*. It is known that he had assisted his co-workers in the animal house during the butchering of a hog which had previously been inoculated with a virulent strain of *Br. melitensis* of caprine origin.

Physical Examination—Examination showed a well developed and moderately well nourished man appearing extremely ill and in a semistuporous condition. The temperature was 39 C (102.2 F), the pulse rate, 92, and the respiratory rate, 22. The mucous membranes were slightly pale and the skin moist. Both eyes showed a marked arcus senilis. The ears, teeth, nose, throat and lymph nodes presented no remarkable abnormalities. There was a slight dulness, with some diminution of breath sounds and coarse, relatively dry râles at the base of the right lung posteriorly. There was no evidence of cardiac disease. There was a moderate generalized arteriosclerosis. The abdomen was somewhat distended but there was no tenderness, and no tumor masses could be felt. The external genitalia appeared normal, examination of the rectum showed a slightly enlarged prostate gland, the extremities were free from edema, and the tendon reflexes were normal.

Laboratory Procedures—On admission the blood count showed red blood cells, 4,250,000 per cubic millimeter, hemoglobin, 70 per cent (Sahli), and leukocytes, 4,120. The differential count showed polymorphonuclear leukocytes, 81 per cent, lymphocytes, 15 per cent, and monocytes, 4 per cent. There appeared to be no other abnormality of the blood.

Roentgen examination of the chest failed to reveal any evidence of pulmonary disease.

The urine showed a faint trace of albumin. The reactions to the Wassermann and Kahn tests of the blood were normal.

On February 13, March 3, March 18 and April 3, blood serum failed to agglutinate the following organisms: *Bacillus typhosus*, *Bacillus paratyphosus A*, *Bacillus paratyphosus B*, *Bacillus enteritidis* and *Bacillus coli*. However, the agglutination tests with *Br. abortus* were as follows. On February 13, complete agglutination was obtained in a dilution of 1:320 and partial agglutination in a dilution of 1:640, similar results were obtained on March 4, 18 and 28. Intracutaneous injections of an extract from *Brucella abortus* were followed by hyperemia and accordingly were considered as giving positive reactions. Samples of venous blood obtained on numerous occasions during the height of the fever were reported as yielding no growth of organisms. A duodenal tube was passed, and when the olive was in place 15 cc. of clear bile was removed. Following this, 25 cc. of 50 per cent magnesium sulphate was injected and, after a free flow of bile was obtained, several specimens were procured by aseptic technic. These specimens failed to yield a growth of *Brucella* organisms following their application to suitable culture mediums. No unusual organisms were isolated.

from repeatedly obtained specimens of urine or stools. A presumptive diagnosis of undulant fever was made, but the diagnosis could not be established with certainty.

Clinical Course and Treatment—During the first month of the patient's stay in the hospital, there was some clinical improvement with a gain in strength. During this month, however, anemia developed in which the red cell count and hemoglobin reached a low level of 2,729,000 cells per cubic millimeter and 48 per cent (Sahl), respectively. On April 10 the patient was given an intravenous injection of 0.4 cc of a lysed vaccine made from cultures of *Br melitensis* and *Br abortus* based on the method of Caronia.⁵ On April 14, an injection of 0.1 cc was given. This treatment was discontinued because of the patient's anemia, and on April 20 he was given a transfusion of 265 cc of whole blood. During the next few weeks there was marked clinical improvement in his condition. The anemia gradually decreased and the leukocytes returned to normal. Throughout his stay in the hospital, the patient's temperature was of the undulating type. Each undulation would slowly rise from about 37 C (98.6 F) to about 40 C and then slowly decrease again to 37 C. Each cycle extended over a period of from eight to twelve days, during which time there was fever, alternating with periods of from two to four days of subnormal or normal temperatures. The undulations of fever gradually subsided, and after the temperature had remained normal for one month, the patient was discharged from the hospital on August 1, nearly six months after entry.

Second Admission—The patient was readmitted on September 14.

History Preceding Second Admission—Following his discharge from the hospital, the patient returned to his home for convalescence. Daily observations of his temperature showed it to be 37 C or less, except for an occasional rise to 37.2 C (98.9 F). Four days before readmission to the hospital while recuperating in the mountains, he fell asleep in the sunshine and was exposed to the sun's rays for about one-half hour. The atmospheric temperature was about 104 F. When he awakened, he felt as though he were "burning up", he had a severe headache and a temperature of 39 C. For the following three days he continued to feel ill, and his temperature remained elevated until he entered the hospital.

Physical Examination—The patient did not appear extremely ill but was somewhat lethargic. The temperature was 39 C, the pulse rate, 90, and the respiratory rate, 22. There was nothing new except a generalized maculopapular, erythematous rash. This rash, which we have observed in other patients with undulant fever, was neither irritative nor painful. The superficial lymph nodes were not enlarged. Neither the spleen nor the edge of the liver could be palpated.

Second Laboratory Examination—Specimens of venous blood were removed on the day of entry and again on the following day. One of these was sent to the laboratory of the hospital and the other to Dr Meyer's laboratory at the Hooper Foundation. Ten days later a report was received from each laboratory stating that *Brucella* organisms had been isolated from both specimens. This organism was later identified as *Br melitensis*.⁶ Other laboratory procedures

⁵ Caronia, J. Nature and Uses of Lysed Typhoid Vaccine, *Am J Dis Child* 39 1 (Jan) 1930.

⁶ According to Dr K. F. Meyer, Miss B. Eddie and Miss Veazie, the strain of *Brucella* isolated from W. O. gave the following reactions: positive stain with thionine (50,000), fuchsin and pyronine, reduction of nitrates, no formation of gas, no hydrogen sulphide, agglutinin absorption of *Br melitensis*, low pathogenicity for monkeys and guinea-pigs, no febrile reaction in monkeys, infection in guinea-pigs with not less than 1,500 organisms.

revealed nothing of significance. A biopsy specimen from one of the lesions in the skin was taken. Cultures of this tissue failed to show any bacterial growth. Microscopic examination showed vascular hyperemia and a slight perivascular infiltration of lymphocytes consistent with a diagnosis of subacute inflammation of the skin.

Clinical Course and Treatment—Twelve days after entrance into the hospital, the patient had a sudden attack of severe, constant pain in the right upper quadrant of the abdomen. There was marked hyperesthesia of the skin to the right of the midabdominal line and between the umbilicus and the right costal margin. There was spasm of the muscles in this region, and pain was elicited on deep palpation. A resistance resembling a cystic mass could be felt in the region of the gallbladder. A presumptive diagnosis of acute cholecystitis was made and the patient was afforded symptomatic relief. Morphine was administered and ice packs were applied locally. Specimens of bile were again removed from the duodenum, but these, as on previous occasions, failed to show bacterial growth on culture.

The patient was held under observation and given symptomatic relief until October 22, four weeks after the onset of the pain in the right upper quadrant. During this time the patient's symptoms referable to the region of the gallbladder had gradually subsided. One month after entry the rash disappeared. He was transferred to the surgical service on Oct 22, 1931, about five weeks after entrance to the hospital.

On October 22, a cholecystectomy was performed by Dr H Glen Bell. The wall of the gallbladder was found to be thickened and there were adhesions binding it to the liver and adjacent duodenum. Several centimeters from the gallbladder in the left lobe of the liver, a small band of adhesions extended to the anterior parietal peritoneum. When this was cut through, a small round nodule about 1 cm in diameter was seen in the parenchyma of the liver. This nodule and a surrounding margin of hepatic tissue were removed. The nodule was a rounded, white, fibrous structure with central softening and a granulomatous appearance. A small bit of semipurulent material was expressed and some of this was prepared for culture.

Microscopic Examination of Tissues (by Dr A H Heald, Department of Pathology)—The sections of the gallbladder showed an eroded mucosa, largely replaced by vascular granulation tissue and diffusely infiltrated by lymphocytes and a few neutrophils and eosinophils. The wall was edematous, and inflammatory cells were infiltrated throughout the fibrous septums. Two small, early granulomatous patches were found, one having a small giant cell of the foreign body type at its center.

The sections from the liver showed a bizarre, destructive, inflammatory process in varying stages. The cellular reactions centered about a granulomatous process 15 mm in diameter, the center of which consisted of puriform material, disintegrating polymorphonuclear leukocytes and cellular debris. This was surrounded by a vascular connective tissue wall, epithelioid cells and lymphocytes, among which might be seen an occasional small multinucleated giant cell. Beyond this central lesion there was an infiltration with lymphocytes and plasma cells about the portal channels with an inflammatory proliferation of the epithelium of the bile ducts. Some of the lesions were in an early stage and showed a few neutrophils and eosinophils in the triad spaces. In the intervening hepatic parenchyma, there were numerous small, discrete, tubercle-like foci which consisted of lymphocytes, epithelioid cells and an occasional small giant cell. All foci were surrounded by a proliferative reaction of fibrous tissue which tended to encapsulate them.



Fig 1—Section of the wall of the gallbladder showing increased vascularity and cellular infiltration

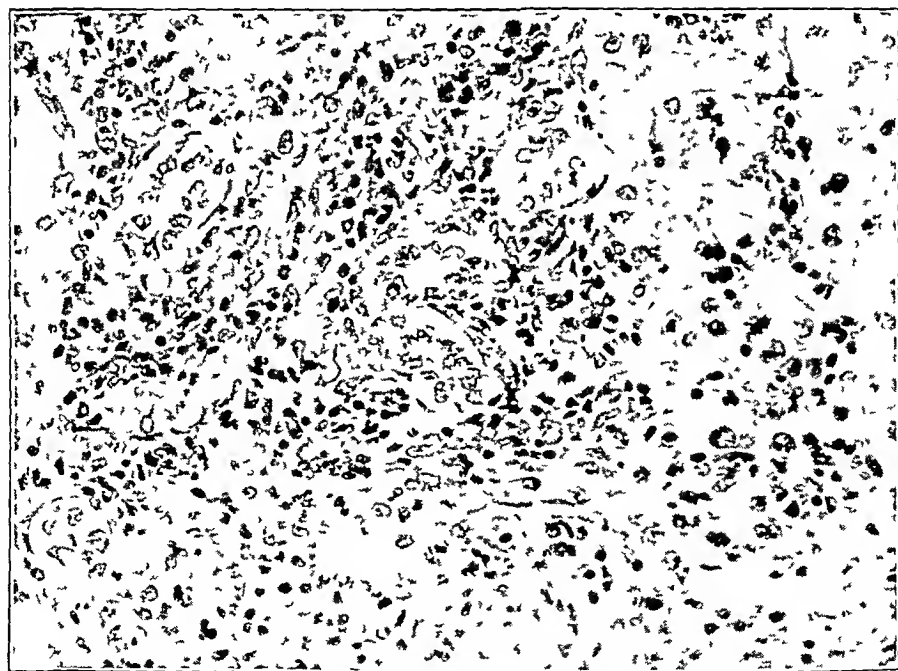


Fig 2—Cellular infiltration in the periportal connective tissue and swollen epithelial cells of the bile ducts

Sections of the wall of the gallbladder and of the granulomatous tissue, fixed in Zenker's fluid, revealed numerous small, gram-negative rods occurring singly and in pairs. In the gallbladder myriads of such organisms were found in the mucosal granulation tissue and throughout the wall. They showed particularly well between the edematous smooth muscle bundles. In the liver the bacilli were found only in the smaller purulent inflammatory zones.

Cultures taken immediately after the removal of the tissues yielded a growth of *Br. melitensis* from both the submucosa of the gallbladder and the granulomatous process in the liver.

Following the operation, the patient's course was uneventful. His temperature returned to normal within a few days and remained so except for an occasional rise in the afternoon to 37.4 C (99.3 F). Cultures of blood, stool and a specimen

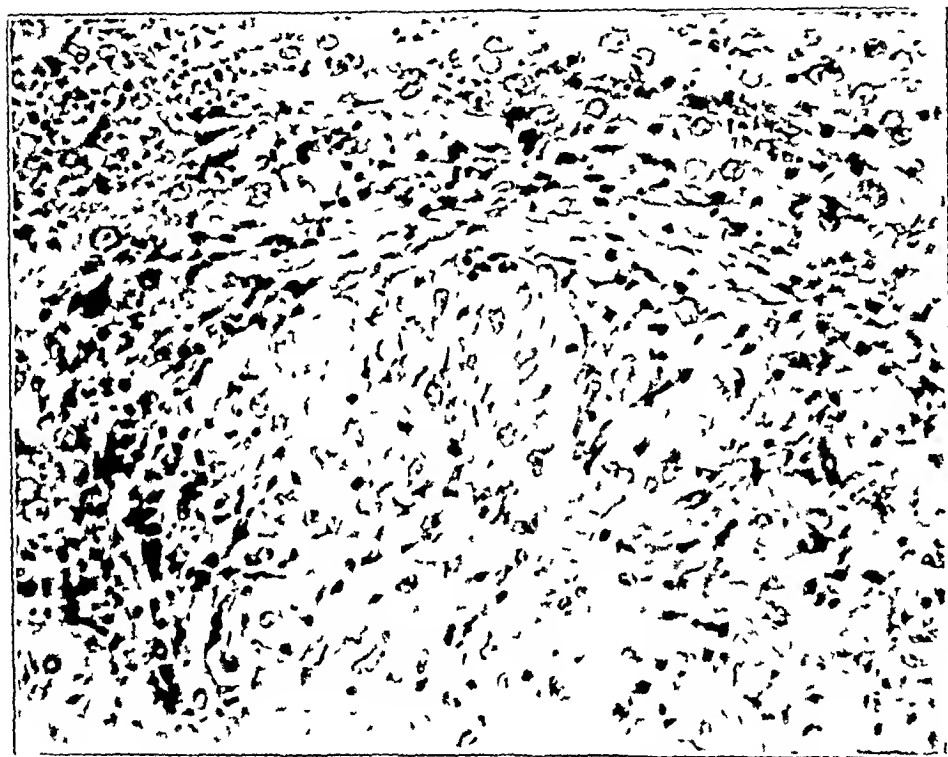


Fig. 3—An early lesion in the hepatic parenchyma adjacent to the main granulomatous nodule. Note the tubercle-like arrangement of epithelioid cells, lymphocytes and fibroblastic tissue. High power.

of bile removed through a duodenal tube on November 23 failed to show a growth of *Brucella* organisms. The patient was discharged from the hospital on November 24. He has had no recurrence of symptoms of active brucellosis up to the present time.

COMMENT

Clinical Features—A diagnosis of this patient's illness was masked during the onset by signs and symptoms suggestive of pneumonia. These disappeared within three weeks' time but the patient's condition continued to be grave and a high fever and leukopenia persisted. A diagnosis of typhoid and paratyphoid infection was practically excluded.

by the laboratory observations. Bacterial endocarditis or other conditions frequently associated with bacteremia were considered unlikely in the absence of petechiae, cardiac signs and the failure to isolate bacteria from the blood stream after repeated attempts. It was believed that the most probable diagnosis was that of undulant fever since on four occasions there was complete agglutination of *Brucella* organisms in a dilution of 1:320, and a partial agglutination in a dilution of 1:640.

The clinical course of the disease was characterized by an undulating type of fever which subsided approximately six months after the onset of illness. The data in the case up to this time were typical of the ordinary form of undulant fever.

The complication in the course of undulant fever presented by this patient occurred after a period of about twelve weeks, during which time his temperature had remained normal. There was a sudden recurrence of the febrile state on exposure to sunlight, and the patient again became critically ill. A diagnosis of undulant fever was confirmed by the isolation of *Br. melitensis* from specimens of venous blood. During this relapse the patient had a sudden attack of severe, constant pain in the right upper quadrant which, along with other signs, was suggestive of acute cholecystitis. At operation the gallbladder was found to be infected, but of considerable additional interest was the finding of a granulomatous process in the liver.

The importance of these structures as a cause of the recurrence of the patient's illness is suggested by his freedom from symptoms relative to brucellosis for a period of two years after their removal.

Pathologic Features—The changes in tissues produced by *Brucella* organisms in animals are well known from studies⁷ made on guinea-pigs experimentally infected with the disease. The organisms become focalized in the liver, spleen and lymph nodes and the cellular reactions about them proceed from those of an exudative inflammatory process to the formation of granulomatous nodules which contain a central necrotic mass. These nodules during the early stages are tubercle-like and consist of lymphocytes, epithelioid cells, an occasional giant cell and a wall made up of connective tissue fibrils. In man, structural changes in the liver, spleen and lymph nodes have been noted as the usual lesions in autopsy material by Gregersen and Lund,⁸ Ebskov and Har-

7 Jaffe, R. H. Ueber die experimentelle Infektion des Meerschweinchens mit dem *Bacillus melitensis* (Bruce) und dem *Bac. abortus* (Bang), *Virchows Arch. f. path. Anat.* **238** 119, 1922.

8 Gregersen, F., and Lund, T. M. De patologisk-anatomiske forandringer ved febris undulans, *Hospitaltid.* **74** 349, 1931.

pøth,⁹ Heiberg,¹⁰ Wohlwill¹¹ and others. It is generally agreed that the nodules appearing in the human viscera are quite similar in their cellular components to those found in the lower animals. It seems apparent in the case reported here that the lesions in the parenchyma of the liver and the wall of the gallbladder were of such granulomatous character.

Final diagnosis of *B. melitensis* as the etiologic factor responsible for these changes in the tissues was established by the growth and identification of these organisms through appropriate cultural and diagnostic methods.

The importance of these pathologic data becomes of greater clinical significance in the light of certain laboratory studies. Kennedy¹² recovered *B. melitensis* in pure culture from the bile in two out of eight cases, while Eyre¹³ stated that the micrococcus might be found in the bile in a "fair proportion of cases." These observations lead to the conclusion that, like typhoid fever, brucellosis in man may be a more frequent predisposing factor in the development of cholecystitis and perhaps cholelithiasis than is generally supposed.

SUMMARY

1. A case of brucellosis in man is reported. The diagnosis during the early course of the disease, although obscure, was suggested by the agglutination of specific antigens and was substantiated later during a relapse by the cultivation of *B. melitensis* from specimens of venous blood.

2. The course of the illness was complicated by the occurrence of cholecystitis and focalized hepatitis. Disappearance of symptoms referable to active undulant fever occurred after the surgical removal of the infected tissue.

3. The local changes in the liver in this case are similar to those produced experimentally in the guinea-pig and rabbit.

4. Attention is called to the possible importance of undulant fever as a predisposing factor in the development of cholecystitis.

9 Ebskov, C., and Harpøth, H. Et tilfælde af febris undulans (Bang), *Ugeskr. f. læger* **37** 872, 1930.

10 Heiberg, S. Nogle tilfælde af febris undulans, *Hospitalstid* **73** 933 (Sept. 18) 1930.

11 Wohlwill, F. Zur pathologischen Anatomie der Bangerkrankung des Menschen, *Virchows Arch. f. path. Anat.* **286** 141, 1932.

12 Kennedy, J. C. Report of the Commission for the Investigation of Mediterranean Fever, 1906, pt. 4, p. 93.

13 Evre, J. W. H. in von Kollé, W. and von Wassermann, A. *Handbuch der pathogenen Mikroorganismen*. Jena: Gustav Fischer, 1912, vol. 4, p. 441.

RELATION OF PORTALS OF ENTRY TO SUB- ACUTE BACTERIAL ENDOCARDITIS

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As part of an investigation in subacute bacterial endocarditis the records of 364 patients admitted to Mount Sinai Hospital in the past fourteen years (to October 1933) have been analyzed, with particular attention to the antecedent history and the manner of onset. Several interesting facts were noted which are reported here.

The outstanding feature of the cases studied is the frequency with which the onset of subacute bacterial endocarditis is associated with an immediately preceding acute infection of the upper respiratory tract, tonsillitis or grip. This relationship has been noted by others. Libman,¹ in an article on the prognosis in subacute bacterial endocarditis, pointed out that the onset can occur with an attack of acute tonsillitis. He also wrote that "there is evidence which indicates that repetition of infection (in cases with recurrent attacks) may be due to an invasion from focal infections." In a subsequent article² he and his co-workers again drew attention to this fact. Oille, Graham and Detweiler,³ in a discussion of the streptococcic bacteremia in endocarditis, pointed out that, in their opinion, endocarditis more frequently follows tonsillitis in children than is commonly believed.

There is also a good deal of bacteriologic and immunologic work which lends evidence to this conclusion. Kreidler,⁴ in a study of the organisms isolated from 14 cases of subacute bacterial endocarditis (13 nonhemolytic streptococci and 1 beta hemolytic strain), pointed out the striking serologic individuality of each of the nonhemolytic organisms. There was no cross agglutination or complement fixation demonstrable, and immune bodies were present in the patients' serum against the homologous invader only. The fermentation reactions also varied.

From the medical service of Dr. B. S. Oppenheimer, the Mount Sinai Hospital.

1 Libman, E. A Consideration of the Prognosis in Subacute Bacterial Endocarditis, *Am Heart J* **1** 25 (Oct.) 1925.

2 Rothchild, M. A., Sacks, B., and Libman, E. The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, *Am Heart J* **11** 356 (April) 1927.

3 Oille, John A., Graham, Duncan, and Detweiler, H. K. Streptococcus Bacteremia in Endocarditis, *J A M A* **65** 1159 (Oct. 2) 1915.

4 Kreidler, W. A. Bacterial Endocarditis. Subacute, *J Infect Dis* **39** 200, 1926.

The same bacteriologic and immunologic heterogeneity exists among the streptococci of the upper respiratory tract. In fact, this is probably the only location in the body in which such a flora is constantly present and which can furnish the necessary nidus and portal of entry for the establishment of an endocardial implantation. The work on the flora of the upper respiratory tract is too voluminous to be quoted in detail. Hooker and Anderson⁵ studied 2,057 colony strains of streptococci from 101 specimens of sputum and reported the dominant aerobic strains to be of the nonhemolytic (alpha) type. Gamma types were also present, but rarely dominant. This parallels the observations on blood cultures in subacute bacterial endocarditis. They also showed the same bewildering heterogeneity among their nonhemolytic (alpha) streptococci that Kreidler noted in his blood cultures. Using cross-agglutination and complement fixation, they found less than 3 per cent which showed any antigenic relationship in 616 tests. No identical strains from different sources were discovered. Arnold⁶ made two series of throat cultures, one three months before and one during an epidemic of influenza. In the first series 134 throats were investigated, of which 91 per cent were found to harbor nonhemolytic streptococci. In the group with influenza 116 cases were studied, and they all yielded, without exception, the nonhemolytic streptococcus.

A good deal of work in this field has been done on extirpated tonsils. Polvogt and Crowe,⁷ in cultures from tonsils following 100 operations, found the alpha and beta types of streptococci in 91 per cent. Bartlett and Pratt⁸ found streptococci present in 75 per cent of their cases, of which 22 per cent revealed the nonhemolytic variety. Kilduffe and Hersohn⁹ studied 409 tonsils and found nonhemolytic streptococci in only 5 per cent. Julianelle,¹⁰ in a similar study, found them in 31 per cent.

This accumulation of clinical and bacteriologic evidence, which can be multiplied, suggests with fair decisiveness that the upper respiratory passages harbor the foci which act as the most common portal of entry in subacute bacterial endocarditis. It also suggests the important con-

5 Hooker, S. B., and Anderson, L. M. Heterogeneity of Streptococci Isolated from Sputum, *J. Immunol.* **16** 281, 1929.

6 Arnold, L. Classification of Streptococci, *J. Lab. & Clin. Med.* **5** 587, 1920.

7 Polvogt, L. M., and Crowe, S. L. Predominating Organisms Found in Cultures from Tonsils and Adenoids, *J. A. M. A.* **92** 962 (March 23) 1929.

8 Bartlett, F. H., and Pratt, J. S. Streptococci Isolated from Excised Tonsils and Posttonsillectomy Blood Cultures, *Am. J. Dis. Child.* **41** 285 (Feb.) 1931.

9 Kilduffe, R. A., and Hersohn, W. W. Cultures of Tonsils, *J. Lab. & Clin. Med.* **12** 788, 1927.

10 Julianelle, L. A. Cultures of Tonsils, *J. Lab. & Clin. Med.* **9** 699, 1924.

clusion that transient bacteremia is not an infrequent occurrence in the apparently benign infections in this region

There are other less common portals of entry. Horder¹¹ in an early communication, wrote that the portal of entry may be not only through the mouth and throat but through the intestinal tract as well. Libman,¹² in discussing "operative bacteremia," the bacteremia established by an operative manipulation or surgical dressing pointed to infections in the male and female genito-urinary tracts and to phlegmons and wounds as a possible portal of entry, and stated that a resulting endocarditis frequently occurs. Thayer¹³ made the important observation that "many instances of endocarditis due to *Streptococcus viridans* owe their origin to pyorrhoëa alveolaris or abscesses about the roots of the teeth." One of our patients gave a history of an immediate preceding infection of a hand, another of an otitic infection, one of a miscarriage, another of a cystoscopy and several of instrumental abortion. The latter cases and the inference that can be drawn from observations on gonorrheal endocarditis lead one to regard the genito-urinary tract as a not uncommon portal of entry for streptococcic endocarditis, probably only second in importance to the upper respiratory tract.

Another significant fact established by the study of our cases is the frequency with which a preexisting pathologic condition of the heart was demonstrated. In almost every case in which an adequate history was available an earlier abnormal cardiac condition was demonstrable. Libman¹ and his co-workers² drew attention to this and indicated that preexisting valvular or myocardial disease is a factor in subacute bacterial endocarditis which needs further study. Horder¹¹ obtained a history of preexisting rheumatic fever in 72 of his 150 cases. Of 118 postmortem examinations 80 per cent revealed preexisting valvular lesions on gross pathologic study. He also noted that a congenital defect predisposes the heart to infection. In the larger number of cases in my series the history was of specific rheumatic fever with cardiac involvement, chorea or typical rheumatic arthritis. In a smaller number atherosclerotic cardiac disease or a congenital anomaly was present. Syphilitic cardiac involvement can also be the precursor of subsequent subacute bacterial endocarditis. This is to be inferred from a case in the series (which came to necropsy), in which an acute endocarditis was engrafted on syphilitic aortitis. Though

11 Horder, Thomas. Infective Endocarditis. *Quart J Med* **11** 319, 1908-1909.

12 Libman E. General Infections by Bacteria, *J Michigan M Soc* **23** 462 (Nov.) 1924.

13 Thayer, W. S. Bacterial (Infective) Endocarditis, *Johns Hopkins Hosp Rep* **22** 173, 1926.

exceptions undoubtedly may be found, it can be accepted as practically axiomatic that subacute bacterial endocarditis requires the fertile soil of an earlier endocarditis, rheumatic, atherosclerotic or syphilitic, or a congenital cardiac lesion on which to implant itself. Libman also included scarlet fever as one of the diseases which may furnish the necessary pathologic state of the heart.

Beside the history of infection of the upper respiratory tract in patients with earlier cardiac disease I have, in several cases, encountered a history of trauma in this region, such as tonsillectomy or extraction of a tooth, which closely antedated the onset of the symptoms. This points to the logical inference that these apparently minor surgical procedures may be accompanied by bacteremia, and in people with earlier cardiac disease result in an endocardial implant. Rushton¹⁴ reported 4 cases of subacute bacterial endocarditis (from a series of 40 studied) in which onset dated from the extraction of a tooth. Bernstein¹⁵ described the case of a young man of 25, with a history of chorea and rheumatic fever, in whom fever and the clinical picture of subacute bacterial endocarditis developed 5 days following the extraction of a tooth.

That surgical intervention in this and other parts of the body is frequently accompanied by bacteremia has been demonstrated. Schwarz and Frisch,¹⁶ in discussing the negative results obtained by Rubin, Epstein and Weiner,¹⁷ reported blood cultures from 11 patients before, during and after tonsillectomy. All the cultures taken before and after operation were sterile. Cultures in 3 cases taken during the operation were positive. One of these showed a hemolytic streptococcus, another an anhemolytic streptococcus and the third a streptococcus which grew in one flask and died in subculture. Dabney¹⁸ reported a streptococcal bacteremia two weeks following a tonsillectomy, the development of an acute infection of the mastoid process which on operation showed only staphylococci, the subsequent development of the picture of a lateral sinus thrombosis followed by negative findings at operation and the ultimate spontaneous recovery of the patient. He assumed that a local infected thrombus in the tonsillar fossa fed into the blood stream.

14 Rushton, M. A. Subacute Bacterial Endocarditis Following Extraction of Teeth, *Guys Hosp Rep* **80** 39 (Jan) 1930.

15 Bernstein, M. Subacute Bacterial Endocarditis Following Extraction of Teeth, *Ann Int Med* **5** 1138 (March) 1932.

16 Schwarz, H., and Frisch, J. A. Blood Cultures After Tonsillectomy, *Am J Dis Child* **38** 1282 (Dec) 1929.

17 Rubin, M. I., Epstein, I. M., and Werner, Marie. Blood Cultures After Tonsillectomy, *Am J Dis Child* **38** 728 (Oct) 1929.

18 Dabney, V. Bacteremia Due to Tonsillectomy Complicated by Mastoiditis, *Arch Otolaryng* **2** 362 (Oct) 1925.

Bacteremia incident to operation in other infected areas has been frequently reported. Seifert¹⁹ reported 9 cases of 43 investigated in which bacteremia was demonstrated during appendectomy. He also obtained 60 per cent positive blood cultures during a series of operations on bone and 40 per cent during a series of operations on soft parts. Harter²⁰ pointed out that a positive blood culture following mastoidectomy is probably common and is not necessarily an indication of lateral sinus thrombosis. Schottmuller²¹ demonstrated the presence of bacteremia during curettage. Libman²² and Libman and Celler²³ described many cases of postoperative bacteremia and bacteremia after trauma.

The demonstration of bacteremia during operation in an infected area led me to determine how many patients in my series dated the onset of symptoms from some form of surgical intervention, particularly in the mouth and throat, such as tonsillectomy or extraction of a tooth. Ten gave such a history. These cases are reported here. In a number of others the history was too inadequate to warrant consideration. In many earlier cases the history of an antecedent operation was not inquired into. The incidence, therefore, of 10 cases in 364 studied is probably much lower than subsequent investigation may show.

The relevant facts in the cases in which an etiology of trauma in the upper respiratory passages is indicated are as follows:

REPORT OF CASES

CASE 1—A girl, aged 21, had chorea at the age of 12 and an attack of rheumatic fever at the age of 15. She was in bed for three months with the latter attack, and was informed that her heart was involved. At the age of 19 she suffered from another attack of rheumatic fever, and was hospitalized for three weeks. Following this she felt well for one and a half years, and was able to carry on fairly strenuous work.

Eighteen months before admission she had a sore throat, following which a tonsillectomy was performed. Since this operation the patient had been growing progressively more weak and tired, she had had transient pains in the legs and back, and her appetite had been poor. For two weeks before admission to the hospital she suffered from a persistent severe headache and for a week had been aware of fever.

19 Seifert, E. Bacteremia After Operations, *Arch f klin Chir* **138** 565 (Oct 20) 1925.

20 Harter, J. H. Significance of Bacteremia Following Mastoid Operations, *Northwest Med* **24** 35 (Jan) 1925.

21 Schottmuller, H. Bacteria in Blood After Curettage for Infected Abortion, *Munchen med Wchnschr* **58** 557, 787, 2051, 2123 and 2170, 1911.

22 Libman, E. On Some Experiences with Blood-Cultures in the Study of Bacterial Infections, *Bull Johns Hopkins Hosp* **17** 215 (July) 1906, The Value of Bacteriological Investigations in Otology with Special Reference to Blood Cultures, *Arch Otol* **37** 22 (Feb) 1908.

23 Libman, E., and Celler, H. L. The Importance of Blood Cultures in the Study of Infections of Otitic Origin, *Am J M Sc* **138** 409 (Sept) 1909.

Physical examination revealed a girl who was obviously chronically ill. There was one petechia on the left shoulder and another in the left lower conjunctiva. Her heart was enlarged, and an accentuated first sound preceded by a rumbling crescendo presystolic murmur was present. This was followed by a loud blowing systolic and a soft diastolic murmur. The urine showed red blood cells on two occasions. The blood culture was positive for anhemolytic streptococci, with 200 colonies per cubic centimeter.

The patient was discharged unimproved.

CASE 2—A woman, aged 30, could not give a satisfactory history, but knew of no specific cardiac disease. She said, however, that she had suffered from dyspnea and palpitation on moderate exertion, such as climbing one flight of stairs. She had had two therapeutic abortions.

Twelve weeks previous to admission she had a tooth extracted, immediately following which she noted general malaise, chilly sensations and fever. Then left nasal hemianopia developed and ten days following the onset of symptoms she had a chill. This was followed by several recurrences. She also had drenching sweats and arthralgia. She noted redness and tenderness of the finger-tips. During the three days before admission, she had two severe attacks of abdominal pain. On admission the patient showed pronounced anemia. There was a petechia in the right lower conjunctiva and a hemorrhage in the disk of the left fundus. The heart was enlarged, and presented the classic murmurs of advanced mitral stenosis and insufficiency. There was also present bilateral costovertebral tenderness, clubbing of the fingers and a *cafe au lait* complexion. The blood culture was positive for *Streptococcus viridans*, with 25 colonies per cubic centimeter.

The patient grew worse rapidly and died. A postmortem examination was not permitted.

CASE 3—A boy, aged 15, four years previous to admission was examined by a doctor on the occasion of a gastric disturbance and was told that he had a cardiac lesion. Otherwise, the boy looked well and gave no evidence of cardiac disability. He had had tonsillitis two years before examination. The history was otherwise irrelevant.

Eight weeks following a tonsillectomy he noted progressive anemia, weakness, emaciation and loss of weight. He recovered sufficiently to return to school for a short period. He soon, however, had to go to bed, with a temperature of 102 F, general malaise, prostration and anorexia. Four weeks previous to admission he had had an attack of motor aphasia which lasted for one day. During the four weeks the renal function had diminished, and he passed only small amounts of highly colored urine. During the same period edema of the face, scrotum and lower extremities had been developing.

On admission he was found to be extremely ill, with marked anemia. He was lethargic and showed edema of the face, legs, scrotum and abdominal wall. There was one petechia present in the left lower eyelid. His heart was enlarged, and a loud double mitral murmur was present. The spleen and liver were palpable. Slight costovertebral tenderness was present and suggestive clubbing of the fingers. The urine contained red blood cells.

The blood culture showed anhemolytic streptococcic (anaerobic) bacteremia.

The patient died after four weeks in the hospital, and the clinical and bacteriologic findings were confirmed at autopsy.

The heart showed subacute bacterial endocarditis involving the mitral valve and the left auricle, with older healed lesions of the interventricular septum and aortic valves.

CASE 4—A woman, aged 25, gave a history of having "caught cold" about seven years earlier, shortly after childbirth. One month later, arthralgia developed in the toes, the pain migrating upward to the ankles and then to the knees. There was no involvement of other joints, and she recalled no redness, swelling or fever. The pain persisted for about a year. Following this dyspnea developed, with attacks of palpitation on moderate exertion. She also had occasional sticking pains over the precordium.

Two months previous to admission she had a molar extracted. The following afternoon she noted chilly sensations, and that evening a fever developed. She had lost 9 pounds (4.1 Kg) in four weeks, and was growing progressively weaker.

The physical examination showed the patient to be an anemic, underweight young woman. A precordial thrill, a sharp systolic impulse and the murmurs of mitral stenosis and insufficiency were present. The spleen was palpable. No embolic phenomena were noted.

The blood culture was positive for *Str. viridans*, with 18 colonies per cubic centimeter.

She had a febrile course, with a temperature up to 102 F, and died after one month in the hospital. Autopsy confirmed the clinical and bacteriologic observations. The mitral valve was tightly stenosed, the cusps were densely fibrotic, and superimposed on the auricular aspect of both cusps there was an irregular, friable, grayish-white, fungoid, bacterial vegetation which was adherent to the leaflet and showed organization.

CASE 5—A man, aged 31, had had acute rheumatic fever seven years previously, which left him with mitral stenosis and insufficiency and a possible aortic insufficiency.

He had been having some arthralgia, and was advised to have several teeth extracted. He followed this advice, and three weeks later noted the onset of fever and sweats. These had continued for four months, up to the time of admission to the hospital. Cachexia had been progressive. Three weeks before admission he noted some painful red spots on the volar aspect of the tips of several fingers, and he also felt a sudden sharp pain in the left upper quadrant of the abdomen.

On admission he appeared to be ill and emaciated. His skin was ashy and mottled in color, a petechia was found in the left supraclavicular region and a Janeway node in the left hypothenar eminence. Marked sternal tenderness was present. The heart was enlarged downward and to the left. A rough systolic and a soft diastolic murmur were audible at the apex. He showed slight clubbing of the fingers, and the spleen was palpable. Red blood cells were found in the urine.

Two blood cultures were positive for *Str. viridans*, with 26 and 30 colonies per cubic centimeter, respectively.

He was discharged after five weeks, unimproved.

CASE 6—A girl, aged 16, was discovered to have a congenital heart lesion at the age of 6. She had three previous admissions to the hospital, the first, seven years before for thrombocytopenic purpura. On her third admission, three years before the last admission, a splenectomy had been performed. She had been free from symptoms since.

Three months before admission the patient had an aching tooth extracted. Four weeks later she began to note fatigue, malaise, blurring of vision and headaches. At about the same time she suffered a sudden and severe abdominal cramp, localized just to the right of the umbilicus. She had a temperature of 100 F and continued to have a fever up to the time of admission. For four days previous to admission she had a dull pain in the left thumb and in the great toe of the right foot.

The essential findings in the physical examination were a loud to-and-fro murmur, a heart enlarged to both the right and the left and sternal tenderness. Two blood cultures showed 150 and 130 colonies of *Str viridans* per cubic centimeter, respectively.

She was discharged after hospitalization for seventeen days, her condition unchanged.

CASE 7—An 8 year old girl, was admitted with a history of chorea, nine months prior to the present admission. The chorea lasted about six weeks, followed by a period of comparative well-being. Five months previously, following the extraction of two teeth she began to have a septic temperature. Associated with this were occasional vomiting and general malaise. Seven weeks before and again six weeks before she was given a transfusion of blood. She showed slight improvement for about two weeks. At this time another tooth was extracted, with a resultant flare-up of temperature to from 102 to 103 F and an increase in her general malaise. Two weeks prior to admission she had two attacks of sharp cramplike pain in the epigastrium. She was reported to have had paralysis of all the extremities at this time, with a gradual clearing up of the condition in three days, only the left arm still showing some weakness. She had been growing progressively weaker, and was admitted for observation.

On admission she presented an acutely ill and septic appearance. There were petechiae on the neck and anterior wall of the chest, some dulness and rales were heard at the base of the right lung anteriorly. The heart was enlarged, a soft systolic murmur was present at the apex, and a harsh impurity of the first sound was heard in the second and third interspaces to the left of the sternum. The liver and spleen were palpable. The neurologic changes suggested left cerebral thrombosis. The blood culture was positive for *Str viridans*.

The child's condition grew worse rapidly, and, she died thirty hours after admission. Postmortem examination was not permitted.

CASE 8—A chauffeur, aged 33, had never had symptoms or signs suggestive of rheumatic fever, chorea or cardiac disease. His family history was irrelevant. He was referred to the hospital with a history of pain in the right lower quadrant of three days' duration, accompanied by a slight fever and marked abdominal tenderness. There had been no vomiting. Acute inflammation of the appendix was considered, and the patient was admitted to the medical service for observation.

Two and one-half months earlier he had a tonsillectomy performed. One week following this profuse sweats began and he noted considerable malaise. No other symptoms developed until two weeks before admission, when he began to have chills and a temperature. Herpes labialis appeared one week before admission.

It was noted on admission that beside the tenderness in the right lower quadrant the spleen was easily palpable and that a rough systolic murmur was audible. Red blood cells were present in the urine. The blood culture showed *Str viridans* bacteremia.

During hospitalization of eight weeks the patient presented numerous embolic phenomena, which included renal infarction, petechiae, lesions of the fundus and an embolus into the right axillary artery, for which an exploratory embolectomy was attempted. The patient died following signs of mesenteric thrombosis.

Autopsy revealed no evidence of rheumatic cardiovalvular disease. There was present, however, a congenital lesion of the aortic valve (a bicuspid aortic valve), with a rudimentary third leaflet, on which the vegetations of the subacute bacterial endocarditis were engrafted. The valve leaflet had been perforated.

CASE 9—A man aged 24, with cardiac disease had been visiting the cardiac clinic for many years. Two years previous to the present admission he had been hospitalized for an attack of acute rheumatic fever with arthritis and further cardiac involvement.

Eleven weeks before admission he had a tooth treated and then extracted. An apical abscess was found. Two weeks following the incident he noted general weakness, malaise and increasing pallor. His condition became progressively worse, and a record of his temperature showed daily rises, on some days up to 101 F. Five weeks before admission a pain developed in the left leg which persisted for six or seven days. One week later a similar pain appeared in the right arm and shoulder, with inability to raise the arm. This also cleared up. Ten days before admission arthralgia developed in the right toe and in the ring fingers of both hands, and four days later a sharp sticking pain appeared in the left upper quadrant of the abdomen. Just before admission he noted orthopnea and nocturnal dyspnea.

Physical examination revealed the patient to be acutely ill, dyspneic and orthopneic, and his temperature 101 F. A petechia was present in the left lower conjunctiva. The heart was enlarged to the right and left, and the murmurs and dynamics of mitral and aortic insufficiency and aortic stenosis were present. There was tenderness in the left upper quadrant of the abdomen. Clubbing of the fingers and hematuria were noted.

The blood culture was positive for *Str. viridans*, with 35 colonies per cubic centimeter. The patient died five weeks after admission. An autopsy was not permitted.

CASE 10—A married woman, aged 33, a quadripara, had had one stillbirth, one spontaneous abortion at ten weeks and two normal deliveries. Eighteen years before admission she had an attack of "tonsillitis," followed by stiffness of both hands and wrists and then of the shoulders. This lasted for three months and recurred twice during the two succeeding years, each attack lasting approximately the same length of time. Eleven years before admission she was told that she had a cardiac murmur. For the preceding eleven years she had had occasional sharp pains to the left of the sternum which came on suddenly and lasted only a few minutes. One year before admission she suffered from an attack of palpitation, with a regular cardiac rate of 150. At this time she was in bed for two weeks. Four weeks following the first attack she had a second. Rest in bed for one day corrected this.

The more immediate history dates back six months previous to admission, when she began to have pain on bending the metacarpal phalangeal joint of the right index finger. This persisted to the time of admission to the hospital. One month before hospitalization she had pain in the left mandibular joint, which lasted for a few days and recurred two weeks later. This was still present at the time of admission, and made chewing painful.

Ten weeks before admission she had all her upper teeth and one of her lower teeth removed. Since then she had lost 8 pounds (3.6 Kg), and for the past six or seven weeks her temperature had been from 100 to 102 F during the day, rising higher during the night. She had a shaking chill lasting from ten to fifteen minutes, seven days before admission. There had been no embolic manifestation and no syncope.

Physical examination revealed the patient to be well developed and well nourished. The upper jaw was edentulous, and only six teeth remained in the lower jaw. The eyes, ears, nose, throat and lungs were essentially normal. The heart was enlarged downward and to the left to the anterior axillary line. There

was prominence of the pulmonary conus. The second pulmonic sound was louder than the aortic. There was a presystolic thrill and a crescendo murmur at the apex. A low systolic murmur was present at the base.

The liver was palpable about 1 cm. below the costal margin, and the spleen could just be felt.

The patient was in the hospital for seven and a half weeks during her first admission. At that time the temperature ranged between 100 and 102 F, occasionally it rose to 103 or 104 F.

The sedimentation time was eighteen minutes. The white blood cell count was 10,000, with 64 per cent polymorphonuclears. The hemoglobin content was 76 per cent. The urine occasionally showed some erythrocytes. Three blood cultures were positive for the alpha streptococcus.

While she was under observation there developed an Osler node on the left great toe, a splenic infarct and clubbing of the fingers. The hemoglobin content dropped to 58 per cent at the time of her discharge.

She was readmitted moribund four months later and died within five minutes. An autopsy was not permitted.

The sequence of events in this case was probably implantation on the endocardium resulting from the dental trauma in a person with rheumatic cardiac disease at a time when she was having a recurrent attack of low grade rheumatic fever.

SUMMARY

Results of a study of 364 cases of subacute bacterial endocarditis suggest that the common portal of entry of the streptococcus is from foci of infection in the passages of the upper respiratory tract and the mouth. Other portals of entry are the genito-urinary tract, otitic infections and wound infections. I have found no evidence of the gastrointestinal tract as the portal of entry in any of the cases. The onset with an acute infection of the upper respiratory tract or tonsillitis in many cases led to the conclusion that in these apparently benign infections a transient bacteremia may occur. The frequency of antecedent cardiac disease, usually rheumatic but sometimes atherosclerotic or syphilitic, or some congenital lesion, indicated that the streptococcus probably requires a previously diseased or abnormal endocardium on which to implant itself.

Ten cases of subacute bacterial endocarditis are reported, in which a history of tonsillectomy or extraction of a tooth closely antedated the onset of symptoms, indicating that trauma of an infective focus about the teeth and pharynx may produce transient bacteremia and thus play a part in promoting implantation on the endocardium.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

III DIETS CONTAINING WHOLE DRIED LIVER, LIVER RESIDUE AND LIVER EXTRACT

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Chanutin and Ferris¹ reduced renal tissue in the rat to a minimum compatible with life and demonstrated a progressive development of polyuria, albuminuria, retention of nitrogen, renal hypertrophy, hypertension and cardiac hypertrophy. The animals were fed a stock diet containing a moderate amount of protein. Wood and Ethridge² reported pathologic changes in the kidney stumps of partially nephrectomized rats. They noted changes in the glomeruli, tubules, small arteries and arterioles. The arterial lesions were similar to those noted in human arteriosclerosis. In the physiologic and pathologic changes that are seen after subtotal nephrectomy, an excellent opportunity is offered for studying the influence of various combinations of foodstuffs and metabolites on the damaged kidney.

The present study was undertaken to ascertain the effect of feeding diets containing whole liver, liver protein and a concentrated aqueous extract of liver to animals with acute and potential renal insufficiency. The degree of renal insufficiency, hypertension and azotemia and the relationship of the size of the heart, kidney and liver to the surface area were studied by the methods described by Chanutin and Ferris¹.

The effect of diets high in protein on the kidneys of experimental animals has been studied by numerous investigators. The literature has been reviewed by Mitchell,³ Bischoff⁴ and others. It is difficult to interpret the results reported, since there were variations in the diets, species of animals, the type and the amount of protein fed, the length of feeding time and the age of the animals. Estimates of the degree of damage to the kidney have been based almost entirely on histopathologic studies, though stress has also been laid on the number of casts in the urine,

This investigation was aided by a grant from the National Research Council From the Laboratory of Physiological Chemistry, the University of Virginia

1 Chanutin, Alfred, and Ferris, E B, Jr. Experimental Renal Insufficiency Produced by Partial Nephrectomy. I Control Diet, Arch Int Med **49** 767 (May) 1932

2 Wood, J E, and Ethridge, C. Proc Soc Exper Biol & Med **30** 1039, 1933

3 Mitchell, H H. J Nutrition **1** 271, 1929

4 Bischoff, Fritz. J Nutrition **5** 431, 1932

albuminuria and changes in the concentration of the nonprotein nitrogenous constituents of the blood

The feeding of diets rich in liver to white rats has consistently produced renal damage. Newburgh and Curtis⁵ and Newburgh and Johnston⁶ demonstrated severe renal lesions in the white rat after feeding them diets containing 40 per cent or more whole dried liver. From their experiments, they believed liver to be the most nephrotoxic of the natural foods studied. Blatherwick and his co-workers⁷ demonstrated marked renal changes in the kidney of unilaterally nephrectomized rats fed a diet rich in whole dried liver. Both Mitchell³ and Newburgh and Johnston⁶ postulated that the renal damage in these cases might have been due to substances present in natural foods other than the protein. The latter workers showed that small quantities of sodium nucleate were capable of producing renal lesions.

The experiments reported in this paper demonstrate that the quantity of whole liver and the type of liver fraction may influence the syndrome noted in partially nephrectomized rats.

EXPERIMENTAL METHODS

The animals were raised in this laboratory. They were maintained on a prepared adequate stock diet until they were between 60 and 70 days old, when subtotal nephrectomy, unilateral nephrectomy or control laparotomy was performed. They were immediately given the experimental diets. A maximum number of six rats were kept in a cage and allowed food and water ad libitum up to the time of death. All animals were killed while in good health at definite intervals, with the exception of a few animals that appeared to be slightly ill, or acutely ill and about to die. No quantitative record of intake of food was attempted.

The details of the experimental procedure have been presented in a previous article,¹ but a brief summary of the methods used will be given here. All animals selected for the experiment were anesthetized with ether for the operation. Subtotal nephrectomy was performed by bringing the left kidney to the surface, placing loops of white cotton thread tightly in position around each pole and then ligating the renal tissue by closing the loops. By this method the circulation of the blood was shut off from about two thirds to three fourths of the left kidney. One week later the right kidney was excised. Unilateral nephrectomy was preceded by bringing the left kidney to the surface, exposing and then replacing it, the right kidney was removed one week later. The control animals underwent the same operative procedure, the kidneys being exposed, handled and replaced.

Twenty-four hour specimens of urine were obtained for the concentration test by placing the rats in individual metabolism cages. Food was withdrawn twenty-four hours before the rat was placed in the metabolism cage in order to eliminate the possible effect of food metabolites on the urinary excretion. Food and water

5 Newburgh, L. H., and Curtis, A. C. Production of Renal Injury in the White Rabbit by the Protein Diet, *Arch. Int. Med.* **42**: 801 (Dec.) 1928.

6 Newburgh, L. H., and Johnston, M. W. *J. Clin. Investigation* **10**: 153, 1931.

7 Blatherwick, N. R., Medlar, E. M., Connolly, J. M., and Bradshaw, P. J. *J. Biol. Chem.* **92**: 1884, 1931.

were withdrawn during the period of the concentration test. In a few cases, indicated in the tables, the concentration test was carried out without the preliminary removal of food. In the estimation of urinary protein heat was applied to cause coagulation, and the coagulum was washed, dried and weighed. All blood pressure readings were obtained by inserting a cannula in the carotid artery. Before inserting the needle the animals were anesthetized with ether. The final blood pressure reading was made while the reflexes were active, but before the animal struggled. Small quantities of blood necessary for the analysis of hemoglobin and nonprotein nitrogen were obtained by clipping the tail. The rat was exsanguinated by cutting the carotid artery. The atria of the heart were removed before weighing, so as to obtain the weight of the ventricles. The kidneys and liver were blotted free from excess blood and weighed immediately after removal. The surface area was calculated from the weight of the intact animal by the formula of Lee⁸.

Eight experimental diets were used. The composition of the diets is shown in table 1. The first six diets differed only in the percental concentration of the whole dried liver, which was the chief source of protein. Hog liver kept in cold

TABLE 1—Composition of Rations

Diet	Concentration of Component in Diet, per Cent								Nitro gen, per Cent
	Dried Whole Liver	Liver Resi due	Liver Ex tract*	Meat Resi due	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mix ture†
L 10	10				62	14	5	5	4
L 15	15				53	18	5	5	4
L 20	20				52	14	5	5	4
L 40	40				30	16	5	5	4
L 60	60				12	14	5	5	4
L 80	80					6	5	5	4
L Res		80				6	5	5	4
L Ext			30	20	37		5	5	4

* Expressed in cubic centimeters.

† From Osborne and Mendel (*J Biol Chem* 37: 572, 1919).

storage was purchased in large quantities. It was ground without the loss of tissue juice, dried in a large steam-heated container and ground to a fine powder. The protein in the seventh diet consisted of the residue of the liver after the water-soluble constituents had been removed. The eighth diet consisted of extracted beef muscle (meat residue) plus a concentrated solution of the water-soluble constituents of hog liver, 1 cc of the extract representing 7.5 Gm of whole liver.

For convenience, numerous abbreviations are used in this article. The first six diets are designated L 10, L 15, seriatim, in accordance with the percentage of the whole dried liver in the diet, the seventh diet, in which liver residue was used, is indicated by L Res, and the eighth diet, in which meat residue plus aqueous liver extract was used, is indicated by L Ext. The ratios of the weights of the heart, kidneys and liver to the surface area are expressed by

$\frac{H W.}{S A}$, $\frac{K W.}{S A}$, and $\frac{L W.}{S A}$, respectively.

A detailed histopathologic study of the kidneys of the killed animals was made by K'ang.⁹

8 Lee, M. O. *Am J Physiol* 89: 24, 1929.

9 K'ang, H. J. Unpublished data.

EXPERIMENTAL RESULTS

Controls—Observations on the intact and on the unilaterally nephrectomized rats are shown in table 2. The urinary volume obtained in

TABLE 2—Normal Values in Control Animals Fed a Variety of Diets

Rats	Renal Condition and Diet	Value	Weight, Gm	Duration of Experiment, Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty Four Hour Urine Concentration Test	
					Surface Area ×100	Surface Area ×100	Surface Area ×100			Volume, Cc	Specific Gravity
8	2 kidneys (L 10)	Minimum	183	35	0.170	0.255	1.97	110	30	0.8	1.0332
		Maximum	262	241	0.180	0.413	2.47	132	52	2.8	1.0629
		Average			0.175	0.369	2.26	121	38	1.4	1.0495
7	1 kidney (L 10)	Minimum	210	28	0.168	0.230	1.94	120	26	0.6	1.0395
		Maximum	336	219	0.206	0.330	2.50	140	64	3.1	1.0571
		Average			0.186	0.273	2.30	127	51	2.0	1.0471
5	2 kidneys (L 15)	Minimum	194	50	0.160	0.357	2.14	112	32	0.2	1.0299
		Maximum	312	230	0.185	0.435	2.82	130	55	4.8	1.0674
		Average			0.177	0.410	2.47	120	45	2.3	1.0466
11	1 kidney (L 15)	Minimum	176	50	0.166	0.211	1.91	114	29	0.6	1.0289
		Maximum	401	289	0.195	0.438	2.61	152	51	5.0	1.0503
		Average			0.178	0.296	2.22	131	41	2.3	1.0522
13	2 kidneys (L 20)	Minimum	167	56	0.170	0.350	1.93	108	27	1.0	1.0333
		Maximum	395	219	0.205	0.496	3.25	154	57	4.7	1.0747
		Average			0.188	0.414	2.55	121	40	2.9	1.0532
10	1 kidney (L 20)	Minimum	174	14	0.156	0.233	1.85	106	27	0.7	1.0398
		Maximum	362	254	0.199	0.344	3.46	130	56	4.6	1.0678
		Average			0.175	0.290	2.52	119	39	2.2	1.0544
13	2 kidneys (L 40)	Minimum	216	47	0.168	0.423	2.62	112	32	1.5	1.0331
		Maximum	385	202	0.203	0.567	3.99	150	55	4.1	1.0740
		Average			0.185	0.491	3.10	131	39	3.1	1.0524
9	1 kidney (L 40)	Minimum	269	14	0.167	0.315	2.34	110	32	1.3	1.0437
		Maximum	364	92	0.205	0.393	3.76	148	45	5.9	1.0778
		Average			0.181	0.344	2.81	123	39	2.7	1.0594
9	2 kidneys (L 60)	Minimum	178	23	0.156	0.417	2.53	110	28	0.9	1.0386
		Maximum	387	185	0.219	0.548	3.48	150	53	3.7	1.0666
		Average				0.185	3.02	127	38	2.4	1.0522
6	1 kidney (L 60)	Minimum	207	15	0.171	0.345	2.58	114	29	0.7	1.0405
		Maximum	332	133	0.192	0.374	3.26	146	48	6.3	1.0734
		Average			0.184	0.359	2.94	129	42	3.5	1.0559
18	2 kidneys (L 80)	Minimum	155	27	0.154	0.447	2.89	106	34	0.6	1.0388
		Maximum	352	331	0.216	0.702	3.82	142	75	4.7	1.0725
		Average			0.181	0.577	3.26	126	53	2.6	1.0561
18	1 kidney (L 80)	Minimum	150	14	0.137	0.316	2.57	103	35	2.0	1.0347
		Maximum	360	204	0.212	0.525	4.16	160	85	8.9	1.0559
		Average			0.180	0.456	3.27	125	47	4.5	1.0412
11	2 kidneys (L Ext 80)	Minimum	150	73	0.155	0.370	2.55	104	38	1.8	1.0387
		Maximum	346	226	0.206	0.765	3.75	132	97	4.2	1.0789
		Average			0.182	0.588	2.95	118	64	2.6	1.0549
17	1 kidney (L Ext 80)	Minimum	127	30	0.141	0.328	1.81	108	34	1.7	1.0343
		Maximum	361	226	0.202	0.632	3.46	144	122	4.7	1.0664
		Average			0.169	0.475	2.80	120	74	3.1	1.0454
8	2 kidneys (L Ext)	Minimum	173	15	0.149	0.445	1.97	110	31	0.6	1.0350
		Maximum	310	176	0.216	0.583	3.02	124	49	3.5	1.0500
		Average			0.179	0.506	2.54	118	41	1.9	1.0563
4	1 kidney (L Ext)	Minimum	147	15	0.148	0.336	1.95	108	40	1.7	1.0367
		Maximum	315	176	0.178	0.365	2.58	126	46	3.0	1.0595
		Average			0.166	0.356	2.28	120	42	2.3	1.0479

the concentration test exceeded 5 cc in only four of the one hundred and sixty-five controls. Although those animals receiving the 10 per cent whole liver diet had an unusually small urinary output, it may be said that in general the urinary volume of the entire series did not vary greatly with the dietary changes. The specific gravity of the urine varied considerably in individual members of the different groups, but

the average specific gravity in any one group was independent of the diet. The group averages fell between 1.0450 and 1.0594. Hence, it will be seen that the volume and the specific gravity of the urine excreted by the intact and unilaterally nephrectomized rats are not appreciably affected by the nephrectomy or the diet.

In a few cases in which a quantitative analysis for urinary protein was carried out, 0.05 Gm. was the maximum found.

Of the eighty-five intact control animals, there were three rats with blood pressure above 140 mm. of mercury. In the case of eighty unilaterally nephrectomized rats, eight animals had elevated blood pressure. The animals with hypertension were uniformly distributed among the various dietary groups. Unilateral nephrectomy apparently increased the tendency toward higher blood pressure.

The average value of the $\frac{H.W.}{S.A.}$ ratio did not change in the controls fed the different diets. Except in younger animals, there was a high degree of correlation between the $\frac{H.W.}{S.A.}$ ratio and the blood pressure reading.

The average values of the $\frac{L.W.}{S.A.}$ ratio were increased in the rats receiving the larger amounts of whole liver in their diets. Those animals on diets that were 40, 60 and 80 per cent whole liver presented definitely fatty livers. Animals receiving the diet containing liver residue had hypertrophy of the liver, but it was not so great as that seen in rats ingesting the diet that was 80 per cent whole liver. The livers of the rats on the diet containing liver residue were not fatty. There was no noticeable change in the size of the livers of the animals receiving the diet containing liver extract.

The value of the $\frac{K.W.}{S.A.}$ ratio was roughly proportional to the amount of total nitrogen present in the diets based on whole dried liver and liver residue. The increase in value of the average weight ratio of the kidneys of the intact control animals receiving 80 per cent whole liver was 56 per cent (0.577) greater than that of controls receiving 10 per cent whole liver (0.369). The liver residue caused a still greater hypertrophy (0.588), owing perhaps, to the greater concentration of total nitrogen. The kidneys of the animals fed the diet rich in liver extract were slightly larger than those of animals fed a diet based on whole liver containing a comparable amount of nitrogen. The degree of renal hypertrophy in the unilaterally nephrectomized rats was greater than that in the intact rats. In fact, the $\frac{K.W.}{S.A.}$ ratio of the group receiving the diet that was 80 per cent whole liver had a value 67 per cent (0.456) greater than that of the group receiving 10 per cent (0.273). The diet containing liver residue was responsible for the greatest hypertrophy (0.475). The renal hypertrophy of the rats fed the liver extract was about equal to that of the rats fed a diet that was 60 per cent whole liver.

Effect of Diet on Experimental Animals—Observations on the partially nephrectomized rats are shown in tables 3 to 10

Because the urinary volume, urinary specific gravity, urinary protein and blood pressure were within fairly fixed limits in all the control animals and did not vary appreciably with the different diets, the following values have been arbitrarily taken as the normal ranges for all animals on which experiments were done urinary volume, from 0 to

TABLE 3—Observations on Partially Nephrectomized Animals Receiving 10 per Cent Whole Liver

Rat	Weight, Gm	Duration of Experiment, Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty-Four Hour Urine Concentration Test		
			Surface Area $\times 100$	Surface Area $\times 100$	Surface Area $\times 100$			Volume Cc	Specific Gravity	Albumin, Gm
1	151	28	0.169	0.174	1.74	130	32	5.0	1.0242	0.006
2	157	28	0.182	0.162	1.93	112	60	2.5	1.0294	
3	170	28	0.183	0.173	1.89	112	48	4.2	1.0229	
4	248	35	0.195	0.156	2.22	122	88	5.1	1.0320	
5	181	65	0.174	0.131	1.86	130	30	4.9	1.0386	
6	155	65	0.194	0.139	1.83	144	53	6.7	1.0204	0.012
7	180	77	0.158	0.170	2.03	116	28	1.8	1.0186	
8	170	77	0.166	0.173	1.79	132		2.5	1.0364	
9	102	77	0.176	0.191	1.95	120	34	2.5	1.0371	
10	174	118	0.177	0.092	2.05	106	42	2.1	1.0410	
11	170	118	0.188	0.157	1.98	124	38	2.5	1.0410	
12	205	118	0.229	0.231	2.13	142	46	3.2	1.0352	
13	208	118	0.205	0.225	2.24	144	32	2.7	1.0435	
14	163	142	0.168	0.174	2.05	120	40	2.5	1.0367	
15	140	142	0.171	0.162	2.20	120	44	1.3	1.0502	
16	150	142	0.180	0.131	1.91	144	45	4.0	1.0243	
17	202	142	0.192	0.193	1.96	146	48	4.6	1.0322	
18	165	142	0.187	0.177	2.22	106	47	2.1	1.0398	
19	171	142	0.170	0.265	2.04	118	44	0.8	1.0696	
20	104	152*	0.242	0.129	1.60	158	60	4.8	1.0219	0.023
21	96	152*	0.216	0.067	1.54	168	100	4.0	1.0229	
22	116	156*	0.242	0.164	1.70	160		3.6	1.0262	
23	172	161	0.177	0.116	1.94	122	46	2.1	1.0275	
24	200	161	0.184	0.197	1.71	134		5.8	1.0268	0.006
25	198	164	0.197	0.193	2.44	130		3.7	1.0290	
26	142	164	0.227	0.160	1.97	202		5.0	1.0251	0.034
27	168	164	0.232	0.164	1.90	206	74	9.5	1.0141	0.020
28	266	166	0.182	0.145	2.34	120	70	4.2	1.0318	
29	215	166	0.193	0.145	2.37	148		4.4	1.0264	
30	143	171	0.256	0.191		164	76	4.7	1.0232	
31	188	171	0.177	0.154	2.18	126	56	1.7	1.0471	
32	162	171	0.197	0.160	2.15	130	62	3.4	1.0360	
33	276	171	0.168	0.165	2.36	118	70	4.4	1.0264	
34	262	219	0.213	0.194	2.06	162	44	3.5	1.0345	
35	166	219	0.197	0.173	1.88	132	40	2.2	1.0297	
36	192	241	0.267	0.234	2.21	168	61	6.5	1.0223	0.000
37	128	241	0.237	0.254	1.70	162	59	7.9	1.0135	0.019

* Acutely ill

5 cc, urinary specific gravity, above 1.0400, urinary protein, from 0.000 to 0.005 Gm and blood pressure, from 100 to 140 mm of mercury. Because the nonprotein nitrogen of the control animals was influenced by the diet, the normal values for the experimental animals were determined by reference to the comparable control group. The heart was considered enlarged when the value of the $\frac{H \cdot W}{S \cdot A}$ ratio was greater than 0.2.

The specific differences apparently due to the different experimental diets are given in detail.

Ten Per Cent Whole Liver (Table 3) The urinary volume was within the normal range in 85 per cent of the animals, 16 per cent excreted between 5 and 10 cc. Despite the small volume of the urine, the specific gravity was low. The largest group (46 per cent) secreted urine with specific gravity between 1.0200 and 1.0300, and 30 per cent between 1.0300 and 1.0400. Only two rats secreted urine with specific gravity below 1.0200. The amount of protein excreted was determined in only eight animals, and the highest value was 0.034 Gm.

Normal blood pressure was seen in 60 per cent of the animals (thirty-seven). Five had blood pressure between 140 and 150 mm up to the one hundred and fifty-second day after operation. At this time, the first readings of definitely increased blood pressure were seen in animals acutely ill (158, 168 and 160 mm). After this period, six of the fifteen rats in good condition had blood pressures above 150, two readings being 202 and 206.

Normal values for nonprotein nitrogen (from 25 to 60 mg per hundred cubic centimeters) were obtained in 74 per cent of the animals. Elevated values were seen during the latter part of the experiment. The highest concentration (100 mg) was seen in an animal acutely ill.

The $\frac{H.W.}{S.A.}$ ratio could be correlated with the blood pressure only after the hundred and fifty-second day. The values of the $\frac{K.W.}{S.A.}$ ratio varied from 0.067 to 0.254. The average value (0.169) was representative of the majority of the kidney stumps. The values of the $\frac{L.W.}{S.A.}$ ratio varied from 1.54 to 2.44 (average, 2.0).

One of the outstanding findings in the study was the long time which elapsed before hypertension developed in these rats. Unquestioned hypertension was first observed about one hundred and fifty days after operation. The volume of urine excreted during the concentration test was small, and the specific gravity was below the value obtained in control animals excreting the same quantity of urine. The nonprotein nitrogen of the blood was variable in amount, but in the majority of cases the value was equivalent to that found in the control animals. The fact that hypertension developed slowly and preceded evidence of renal damage must be considered as an important finding.

Fifteen Per Cent Whole Liver (Table 4) The volume of urine excreted was within the normal range (from 0 to 5 cc) in 48 per cent of the animals. Slightly increased amounts (from 5 to 8 cc) were secreted by 43 per cent. Only three of the fifty-eight rats secreted more than 8 cc, the highest value being 11.6 cc. For the majority of the rats (52 per cent) the specific gravity was between 1.0200 and 1.0300, for 14 per cent between 1.0100 and 1.0200, and for 19 per cent between 1.0300 and 1.0400. The specific gravity seemed to be related roughly to the volume of urine. The protein excreted in the urine varied between 0.002 and 0.112 Gm, 50 per cent of the values were between 0.000 and 0.050 Gm, and 50 per cent were above this range.

Normal blood pressure was seen in 52 per cent of the animals (sixty-four). Of those killed between the forty-eighth and fifty-eighth days after operation, seven of seventeen had blood pressure above 140 mm, the highest value being 192 mm. Between the hundred and fifteenth and two hundred and eighty-ninth days, four of the forty-seven had hypertension. It was possible to group the

rats with hypertension as follows from 140 to 150, 14 per cent, from 150 to 160, 12 per cent, from 160 to 180, 17 per cent, and three had a pressure of 186, 190 and 192 mm, respectively

TABLE 4—*Observations on Partially Nephrectomized Animals Receiving 15 per Cent Whole Liver*

Rat	Weight, Gm	Duration of Experiment, Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty Four Hour Urine Concentration Test		
			Surface Area ×100	Surface Area ×100	Surface Area ×100			Volume Cc	Specific Gravity	Albumin, Gm
1	164	48	0 202	0 179	2 15	156	51	3 7	1 0236	
2	282	48	0 201	0 224	2 49	130	45	3 4	1 0450	
3	172	48	0 208	0 171	1 95	150	60	3 2	1 0351	
4	184	48	0 192	0 156	2 25	138	57	4 2	1 0323	
5	104	50	0 163	0 123	1 44	178	63	3 8	1 0225	
6	200	50	0 184	0 173	2 20	126	57	4 9	1 0261	
7	258	50	0 216	0 199	2 23	162	53	5 1	1 0308	
8	156	50	0 175	0 185	1 92	124	38	1 3	1 0420	
9	144	50	0 218	0 197	1 59	192		5 8	1 0211	
10	190	53	0 183	0 159	2 16	124	59	5 3	1 0251	
11	154	53	0 174	0 178	2 00	160	54	2 1	1 0449	
12	154	53	0 172	0 175	1 99	148	63	4 0	1 0244	
13	232	53	0 187	0 168	2 23	134	48	3 0	1 0416	
14	180	53	0 222	0 216	2 45	136	41	7 5	1 0192	
15	152	53	0 183	0 160	1 85	132	56	7 2	1 0190	
16	218	53	0 172	0 163	2 30	130	48	3 1	1 0101	
17	156	53	0 177	0 138	2 15	122	45	3 0	1 0304	
18	162	115	0 201	0 249	2 20	144	92			
19	113	115*	0 247	0 230	1 64	154	108			
20	150	139	0 161	0 152	1 55	114	52			
21	232	143	0 181	0 219	2 38	120	67			
22	228	143	0 223	0 177	2 17	144	83	7 4	1 0239	0 102
23	192	143	0 178	0 199	2 05	118	47	1 6	1 0500	
24	146	148	0 185	0 160	1 89	134	53	0 6	1 0141	0 006
25	182	148	0 178	0 148	1 63	102	43	7 9	1 0239	0 002
26	228	148	0 172	0 167	2 12	132	31	6 9	1 0288	0 016
27	266	148	0 182	0 194	1 85	186	39	3 5	1 0397	
28	162	154	0 216	0 179	2 08	160	40	6 8	1 0232	0 056
29	168	154	0 211	0 201	1 61	156	48	5 3	1 0237	0 030
30	184	154	0 194	0 177	2 18	126	46	3 2	1 0315	
31	364	158	0 192	0 197	2 38	122	39	3 5	1 0414	
32	218	158	0 210	0 264	2 42	154	57	7 5	1 0260	0 079
33	312	158	0 200	0 206	2 21	134		6 2	1 0291	0 048
34	122	160	0 233	0 128	1 58	160	66	7 5	1 0150	0 010
35	224	160	0 227	0 253	1 88	134	45	7 0	1 0220	0 055
36	148	173	0 189	0 244	1 88	170	72	7 5	1 0220	0 065
37	144	173†	0 193	0 164	2 00	150	42			
38	150	173*	0 231	0 242	1 94	162				
39	210	180	0 192	0 174	2 10	170	55	2 1	1 0119	
40	178	180	0 205	0 216	2 05	174	55	1 3	1 0375	
41	244	180	0 163	0 157	2 02	124	50	5 8	1 0221	0 009
42	250	180	0 206	0 191	2 37	138	56	4 3	1 0305	
43	158	180	0 153	0 134	1 87	118	52	2 3	1 0280	
44	226	180	0 167	0 186	2 10	124		2 2	1 0228	
45	270	188	0 205	0 177	2 13	140	59	2 9	1 0419	
46	200	193	0 237	0 195	2 04	174	63	11 6	1 0101	0 050
47	238	193	0 189	0 199	2 00	140	48	3 7	1 0305	
48	146	198*	0 270	0 258	2 05	172	70	7 0	1 0205	0 017
49	274	198	0 189	0 245	2 01	136		4 2	1 0256	
50	230	198	0 231	0 199	2 01	190		5 5	1 0232	0 027
51	316	198	0 204	0 210	2 42	124	56	2 7	1 0373	
52	190	257	0 201	0 262	2 29	138	50	3 5	1 0296	
53	244	275	0 247	0 266	1 94	186	86	7 0	1 0210	0 010
54	170	275	0 216	0 286	1 81	168	63	8 0	1 0180	0 056
55	184	280	0 184	0 196	2 20	164	48	5 7	1 0241	0 077
56	246	280	0 202	0 212	2 12	152	59	8 0	1 0229	0 056
57	150	280	0 218	0 252	1 95	140	14	6 9	1 0217	0 074
58	168	280	0 194	0 216	2 08	146	65	6 8	1 0218	0 056
59	186	280	0 197	0 202	2 27	150	50	7 5	1 0251	0 092
60	286	280	0 185	0 198	2 24	144	48	5 5	1 0287	0 049
61	220	289	0 229	0 269	2 13	176	76	8 3	1 0207	0 112
62	180	289	0 236	0 213	2 18	124	73	6 4	1 0192	0 010
63	192	289	0 173	0 202	2 38	134	42	3 2	1 0325	
64	210	289	0 209	0 256	2 17	150	49	8 4	1 0190	0 070

* Acutely ill

† Slightly ill

Normal values for nonprotein nitrogen were obtained in 72 per cent of the rats. The highest value (108 mg) was seen in an animal acutely ill.

Forty-seven per cent of the animals had values for the $\frac{H W}{S A}$ ratio above 0.2. The majority had hypertension. The values of the $\frac{L W}{S A}$ ratio varied between 1.44 and 2.49 (average, 2.06). The values of the $\frac{K W}{S A}$ ratio varied between 0.123 and 0.28 (average, 0.216). Both these average values were fairly representative.

Within sixty days after partial nephrectomy, a number of rats showed well marked hypertension. This is rather striking in view of the long latent period before the appearance of hypertension in the animals receiving the diet that was 10 per cent whole liver.

The second largest percentage of animals with normal urinary output was seen in this group. The output of urinary protein was higher than with the previous diet. The retention of nitrogenous materials was not marked. In other words, on this diet hypertension developed sooner, and evidence of mildly decreased function of the kidney made its appearance.

Twenty Per Cent Whole Liver (Table 5) The urinary volume in 28 per cent of the rats was within normal limits (from 0 to 5 cc). Slightly increased amounts (from 5 to 8 cc) were excreted by 39 per cent of this group, and 11 per cent excreted from 8 to 10 cc. A significant effect of this diet was manifested by the increase in the number (18 per cent) excreting between 10 and 15 cc of urine. Two excreted 17.8 and 18.1 cc. The rats were grouped with respect to specific gravity of the urine as follows: from 1.0100 to 1.0200, 16 per cent, from 1.0200 to 1.0300, 39 per cent, from 1.0300 to 1.0400, 31 per cent, and above 1.0500, 6 per cent. With respect to urinary protein, they were grouped as follows: from 0.000 to 0.050 Gm, 21 per cent, from 0.050 to 0.100 Gm, 35 per cent, from 0.100 to 0.150 Gm, 30 per cent, and from 0.150 to 0.226 Gm, 12 per cent. One animal excreted 0.319 Gm.

Fifty-seven per cent of this group (sixty-one) had normal blood pressure. The first increased blood pressure (170 mm) was noted on the forty-fourth day. Those with increased blood pressure were grouped as follows: from 140 to 150 mm, 13 per cent, from 150 to 160 mm, 8 per cent, from 160 to 180 mm, 13 per cent, and from 180 to 200 mm, 8 per cent.

The nonprotein nitrogen values continued to remain relatively low. The majority (68 per cent) showed no retention, 25 per cent had slightly increased values (from 60 to 80 mg), and in only one case was there a value above 100 mg per hundred cubic centimeters.

The values of the $\frac{H W}{S A}$ ratio were above 0.2 in 46 per cent of the rats. This ratio did not appear to be related to the blood pressure during the first five months after the operation. Excessively high values (above 0.3) were obtained in three cases. The values of the $\frac{L W}{S A}$ ratio varied from 1.82 to 2.92 (average, 2.27). Those of the $\frac{K W}{S A}$ ratio varied from 0.149 to 0.423 (average, 0.252). After the seventy-third day the values were consistently increased.

The addition of a relatively small amount (5 Gm) of whole dried liver to the preceding diet seemed responsible for an appreciable increase in the degree of polyuria and the excretion of urinary protein. How-

ever, there was little difference in the occurrence and extent of hypertension. The first case of hypertension was seen on the forty-fourth day after operation. After this, high blood pressure was noted at frequent intervals. The animals in this group showed no striking changes in the degree of retention of nitrogen in the blood. The group was characterized by frequent evidence of increased functional impairment and little increase in hypertension.

TABLE 5—*Observations on Partially Nephrectomized Animals Receiving 20 per Cent Whole Liver*

Rat	Weight, Gm	Duration of Experiment, Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty Four Hour Urine Concentration Test		
			Surface Area ×100	Surface Area ×100	Surface Area ×100			Volume, Cc	Specific Gravity	Albumin, Gm
1	170	14	0.177	0.163	2.32	112	52	4.9	1.0301	
2	154	14	0.169	0.173	1.82	140	66	14.0	1.0158	0.024
3	203	14	0.162	0.184	2.38	118	27	1.3	1.0323	
4	212	14	0.166	0.172	2.24	124	45	5.3	1.0297	0.017
5	177	14	0.163	0.149	2.06	142	27	3.4	1.0307	
6	230	44	0.213	0.261	2.13	120	49	8.7	1.0298	0.111
7	232	44	0.199	0.210	2.09	170	58	7.8	1.0273	0.003
8	121	56	0.162	0.176		120		1.6	1.0418	
9	152	56	0.180	0.203		123		4.8	1.0339	
10	221	60	0.218	0.298	2.68	132	63	14.6	1.0218	0.310
11	269	64	0.185	0.228	2.23	132	50	5.6	1.0299	0.001
12	297	64	0.188	0.203	2.35	136	44	5.4	1.0363	0.020
13	147	69	0.191	0.199	1.95	158	62	7.9	1.0203	0.042
14	121	69	0.312	0.189	2.30	188	87	9.9	1.0197	0.096
15	139	69	0.205	0.210	2.08	140	40	3.6	1.0279	
16	202	73	0.210	0.380	2.01	140	62	11.7	1.0169	0.056
17	189	73	0.242	0.242	2.53	200	42	8.6	1.0271	0.147
18	204	73	0.208	0.235	2.75	144	30	5.8	1.0348	0.128
19	200	110	0.236	0.352	2.01	154	85	12.2	1.0241	0.226
20	168	126	0.215	0.272	2.04	194	60	4.5	1.0384	
21	221	126	0.326	0.310	1.96	190	93	8.2	1.0250	0.130
22	225	127	0.210	0.238	1.94	200	72	11.0	1.0232	0.122
23	310	144	0.312	0.234		170		14.7	1.0149	0.074
24	335	157	0.192	0.209	2.46	136	33	4.0	1.0359	
25	183	157	0.193	0.279	2.34	154	49	7.7	1.0276	0.173
26	211	157	0.188	0.270	2.42	144	61	7.0	1.0266	0.108
27	232	157	0.185	0.212	2.27	134	31	2.3	1.0343	
28	219	158	0.173	0.206	2.23	134	32	2.0	1.0418	
29	198	158	0.176	0.214	2.08	126	31	0.6	1.0567	
30	349	158	0.173	0.218	2.56	120	32	8.5	1.0441	0.012
31	341	175	0.221			174	48	5.5	1.0348	0.114
32	320	180	0.199	0.343	2.24	122	59	6.8	1.0258	0.104
33	311	180	0.175	0.220	1.90	118	30	3.5	1.0331	
34	313	180	0.192	0.231	2.01	140	31	2.7	1.0307	
35	280	180	0.142	0.202	1.83	126	33	2.5	1.0374	
36	247	182	0.211			168	57	7.4	1.0270	0.177
37	340	196	0.215	0.389	2.60	164	56	6.5	1.0418	0.117
38	325	196	0.207	0.269	2.36	132	41	8.0	1.0298	0.080
39	214	196	0.226	0.329	2.60	176	90	17.8	1.0153	0.110
40	350	196	0.200	0.272	2.92	114	44	11.2	1.0284	0.202
41	388	197	0.248	0.312	2.15	176	70	14.9	1.0197	0.097
42	210	197	0.157	0.190	1.91	144	34	2.2	1.0419	
43	308	197	0.199	0.298	2.59	112	49	5.4	1.0361	0.055
44	318	201	0.202	0.272	2.59	122	59	6.4	1.0339	0.145
45	210	201	0.159	0.200	2.31	136	55	3.7	1.0319	
46	234	201	0.183	0.222	2.40	122	52	6.3	1.0289	0.115
47	308	216	0.201	0.248	2.42	144	46	5.5	1.0351	0.101
48	232	216	0.183	0.244	2.19	130	47	9.3	1.0164	0.049
49	365	219	0.211	0.276	2.30	116	64	5.5	1.0334	
50	250	220	0.262	0.290	2.35	170	121	18.1	1.0169	0.221
51	318	226	0.211	0.264	2.28	144	69	11.3	1.0210	0.056
52	202	226	0.210	0.423	2.38	156	72	9.9	1.0175	0.062
53	258	226	0.197	0.240	2.03	126	61	12.0	1.0210	0.056
54	246	226	0.256	0.321	2.46	166	76	6.3	1.0222	0.053
55	308	254	0.175	0.319	2.32	130	50	6.3	1.0300	0.072
56	300	254	0.208	0.294	2.31	124	37	2.2	1.0499	
57	260	254	0.212	0.330	2.08	138		12.0	1.0189	0.060
58	192	254	0.171	0.273	2.28	128	63	6.0	1.0231	0.090
59	276	254	0.202	0.239	2.33	152	59	7.1	1.0237	0.063
60	315	254	0.198	0.253	2.53	120		7.3	1.0274	0.073
61	274	254	0.201	0.248	2.30	146	55	5.9	1.0332	0.080

Forty Per Cent Whole Liver (Table 6) The urinary volume was within the normal range in 12 per cent of the animals. The rats secreting amounts greater than normal were grouped as follows: from 5 to 10 cc, 31 per cent, from 10 to 15 cc, 39 per cent, and from 15 to 20 cc, 15 per cent. Two rats excreted 207 and 21 cc. According to the specific gravity of the urine, the groups were from

TABLE 6—*Observations on Partially Nephrectomized Animals Receiving 40 per Cent Whole Liver*

Rat	Weight, Gm	Duration of Experiment, Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty-Four Hour Urine Concentration Test		
			Surface Area ×100	Surface Area ×100	Surface Area ×100			Volume Cc	Specific Gravity	Albumin, Gm
1	222	14	0.175	0.188	2.07	162	69	14.3	1.0299	0.020
2	210	17	0.152	0.205	2.18	118	68	11.2	1.0239	0.022
3	179	17	0.161	0.202	2.40	116	59	4.5	1.0363	
4	180	17	0.153	0.216	2.05	126	57	3.5	1.0364	
5	149	17	0.138	0.151	2.33	126	60	5.4	1.0315	0.015
6	195	17	0.151	0.173	2.29	114	53	9.1	1.0298	0.017
7	105	17	0.129	0.116	2.16	120	63	7.9	1.0236	0.008
8	299	44	0.213	0.355	3.54	126	56	8.5	1.0317	0.080
9	203	44	0.208	0.295	2.91	124	97	19.0	1.0196	0.213
10	206	44	0.223	0.313	3.24	132	56	4.5	1.0334	
11	250	44	0.187	0.323	2.94	138	77	11.3	1.0252	0.119
12	215	47	0.184	0.304	2.29	164	71	8.3	1.0252	0.140
13	256	47	0.174	0.258	2.41	126	44	5.7	1.0413	0.018
14	214	47	0.159	0.286	2.24	140	45	5.4	1.0379	
15	157	47	0.203	0.271	2.04	174	80	9.5	1.0231	0.104
16	209	47	0.187	0.313	2.22	126	82	11.4	1.0267	0.187
17	261	50	0.203	0.285	2.78	123	63	5.8	1.0367	
18	234	50	0.190	0.266	2.77	130	58	3.2	1.0434	
19	240	50	0.180	0.260	2.50	132	53	4.5	1.0399	
20	247	51	0.227	0.468	2.34	152	89	13.9	1.0258	0.202
21	227	72	0.240	0.280	2.35	186	125	20.7	1.0136	0.093
22	175	72	0.225	0.420	2.53	176	91	17.0	1.0195	0.372
23	241	72	0.204	0.365	2.31	153	98	12.7	1.0190	0.035
24	199	78	0.191	0.360	2.46	150	64	11.4	1.0180	0.065
25	193	78	0.179	0.272	2.28	114	56	13.2	1.0192	0.136
26	293	87	0.231	0.744	2.47	212	106	17.6	1.0200	0.186
27	210	87	0.198	0.464	2.92	146	70	11.3	1.0207	0.127
28	197	92	0.181	0.319	1.92	134	100	11.9	1.0187	0.033
29	183	92	0.222	0.392	2.82	163	104	10.7	1.0212	0.120
30	212	92	0.264	0.618	2.78	178	104	13.5	1.0202	0.114
31	237	92	0.234	0.372	2.55	170	88	10.0	1.0272	0.145
32	153	92	0.255	0.623	3.47	144	119	13.7	1.0193	0.163
33	208	112	0.185	0.256	2.91	134	58	11.7	1.0179	0.059
34	311	125	0.309	0.882	2.68	150	63	12.0	1.0235	0.093
35	189	142	0.248	0.403	2.39	130	90	11.5	1.0227	0.092
36	373	148	0.204	0.435	2.85	154	71	16.4	1.0229	0.080
37	200	148	0.222	0.568	3.28	176	132	13.5	1.0192	0.184
38	295	148	0.203	0.442	2.47	132	89	17.7	1.0200	0.186
39	289	160	0.182	0.251	2.49	133	44	5.8	1.0308	0.066
40	321	160	0.171	0.304	2.77	136	59	8.8	1.0298	0.188
41	271	160	0.191	0.364	2.59	136	62	3.8	1.0265	0.183
42	227	160	0.185	0.446	2.33	180	103	11.6	1.0229	0.204
43	345	160	0.234	1.020	2.18	196	145	18.2	1.0155	0.078
44	304	160	0.230	0.518	2.39	156	106	15.8	1.0117	0.163
45	255	160	0.178	0.290	1.98	154	105	21.0	1.0136	0.059
46	330	184	0.193	0.467	2.38	136	86	10.0	1.0251	0.214

1.0100 to 1.0200, 28 per cent, from 1.0200 to 1.0300, 48 per cent, and from 1.0300 to 1.0400, 20 per cent. Two animals excreted urine with specific gravity above 1.400. According to urinary protein, the groups were as follows: from 0.000 to 0.05 Gm, 21 per cent, from 0.05 to 0.1 Gm, 26 per cent, from 0.1 to 0.15 Gm, 21 per cent, from 0.15 to 0.2 Gm, 20 per cent, and from 0.2 to 0.214 Gm, 10 per cent, and one rat excreted 0.372 Gm.

Animals with normal blood pressure comprised 54 per cent of this group (forty-six). The first rat with hypertension was seen on the fourteenth day, and the next on the forty-seventh day. The animals with hypertension were grouped

as follows from 140 to 160 mm, 20 per cent, from 160 to 180, 20 per cent, and three had pressures above 180 mm

Fewer animals (28 per cent) in this group had a normal concentration of nonprotein nitrogen than in the preceding groups. Those with retention were grouped as follows from 60 to 80 mg, 28 per cent, from 80 to 100 mg, 22 per cent, and from 100 to 150 mg, 22 per cent

The $\frac{H W}{S A}$ ratio was normal in 46 per cent of this group. There was a poor relationship between the $\frac{H W}{S A}$ ratio and the blood pressure. The values of the $\frac{L W}{S A}$ ratio varied between 1.92 and 3.42 (average, 2.52). The values of the $\frac{K W}{S A}$ ratio varied between 0.116 and 1.02 (average, 0.361).

A striking contrast between the rats receiving this diet and those receiving the preceding diets was manifested in the change in urinary volume. There was a definite and rather marked increase in the volume of urine excreted during the concentration test. The specific gravity of these specimens was lower. The albumin excreted was only slightly greater. Retention of nitrogen was more marked and frequent in those receiving the diet richer in nitrogen. Despite the fact that the renal function appeared to be more seriously damaged in these rats, there was little effect on the occurrence, incidence and distribution of hypertension.

Sixty Per Cent Whole Liver (Table 7) The volume of urine excreted was within normal range in 24 per cent of the animals. Those with volumes above normal were grouped as follows from 5 to 10 cc, 20 per cent, from 10 to 15 cc, 34 per cent, and from 15 to 20 cc, 20 per cent. One animal excreted 20.5 cc. With respect to the specific gravity of the urine the rats were grouped as follows from 1.0100 to 1.0200, 32 per cent, from 1.0200 to 1.0300, 38 per cent, from 1.0300 to 1.0400, 28 per cent. The urine of one animal had a specific gravity above 1.0400. With respect to the urinary protein excreted, the rats were grouped as follows from 0.000 to 0.05 Gm, 23 per cent, from 0.05 to 0.1 Gm, 28 per cent, from 0.1 to 0.15 Gm, 21 per cent, from 0.15 to 0.2 Gm, 21 per cent, and from 0.2 to 0.25 Gm, 7 per cent.

Animals with normal blood pressure comprised 45 per cent of this group (fifty-one). The first rat with hypertension was noted on the twenty-third day after the operation, and increased blood pressure was seen at frequent intervals after this. The rats with hypertension were grouped as follows from 140 to 160 mm, 31 per cent, from 160 to 180 mm, 16 per cent, and from 180 to 200 mm, 8 per cent.

Twenty-eight per cent of this group had concentrations of nonprotein nitrogen within the normal range. Those with retention were grouped as follows from 60 to 80 mg, 16 per cent, from 80 to 100 mg, 18 per cent, and from 100 to 150 mg, 34 per cent. Two rats had concentrations of 186 and 174 mg, respectively.

The values of the $\frac{H W}{S A}$ ratio were above 0.2 in 33 per cent of the cases. There was a poor relationship between the $\frac{H W}{S A}$ ratio and blood pressure up to the ninety-second day. The values of the $\frac{L W}{S A}$ ratio varied between 1.85 and 3.28 (average, 2.52). The values of the $\frac{K W}{S A}$ ratio varied between 0.177 and 0.71 (average, 0.41).

The only significant difference present in this group was in the increased frequency of retention of nitrogen. This fact could not be correlated with the damage to the kidney as judged by the concentra-

TABLE 7—*Observations on Partially Nephrectomized Animals Receiving 60 per Cent Whole Liver*

Rat	Weight, Gm	Duration of Experiment Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty-Four Hour Urine Concentration Test		
			Surface Area $\times 100$	Surface Area $\times 100$	Surface Area $\times 100$			Volume Cc	Specific Gravity	Albumin, Gm
1	156	15	0.171	0.209	2.72	112	96	7.7	1.0283	0.035*
2	200	15	0.173	0.261	2.20	104	129	20.5	1.0153	0.018*
3	155	23	0.149	0.197	1.85	130	123	10.2	1.0204	0.025*
4	141	23	0.160	0.215	2.39	138	49	4.2	1.0363*	
5	161	23	0.162	0.238	2.25	156	119	4.2	1.0411*	
6	123	23	0.141	0.177	2.02	134	85	8.0	1.0241	0.111*
7	149	23	0.160	0.229	2.20	122	110	8.1	1.0271	0.068*
8	201	39	0.194	0.345	2.58	170	98	14.5	1.0229	0.194
9	188	39	0.169	0.290	2.60	116	66	7.0	1.0337	0.086
10	195	39	0.171	0.220	2.70	126	44	10.1	1.0248	0.008
11	170	41	0.180	0.404	2.54	144	98	13.1	1.0207	0.157*
12	198	47	0.194	0.300	2.76	156	51	7.4	1.0344	0.075*
13	201	47	0.193	0.373	2.95	136	50	11.6	1.0274	0.192*
14	202	69	0.162	0.416	2.11	148	104	13.9	1.0169	0.049
15	267	69	0.187	0.562	2.21	142	95	11.9	1.0217	0.069
16	178	92	0.233	0.710	2.25	190	132	14.0	1.0165	
17	189	93	0.213	0.771	2.78	148	88	10.0	1.0241	0.235
18	174	102	0.213	0.480	2.40	146	126	11.2	1.0154	0.049
19	278	105	0.219	0.790	2.59	166	186	19.2	1.0154	0.136
20	285	107	0.199	0.218	2.54	146	71	16.5	1.0245	0.197
21	196	112	0.196			140		6.8	1.0262	0.060
22	311	117	0.207	0.660	2.61	138	85			
23	253	128	0.234	0.546	2.42	154	104	14.5	1.0174	0.080
24	191	128	0.221	0.373	2.20	186	109	14.0	1.0172	0.094
25	303	123	0.246	0.425	2.54	152	127	15.8	1.0169	
26	270	133	0.187	0.409	2.90	120	66	8.6	1.0300	0.118
27	183	134	0.210	0.341	2.79	118	72	5.5	1.0322	0.025
28	203	134	0.185	0.484	2.76	172	83	8.5	1.0263	0.125
29	170	134	0.194	0.339	2.62	138	56	4.5	1.0295	
30	201	134	0.208	0.527	2.54	190	119	15.0	1.0193	0.149
31	225	134	0.169	0.311	2.63	120	47	3.3	1.0393	
32	162	139	0.165	0.302	2.11	150	143	10.5	1.0177	0.028
33	207	142	0.193	0.370	2.67	156	68	5.5	1.0342	0.091
34	203	142	0.194	0.598	2.58	172	148	19.6	1.0162	0.168
35	200	142	0.202	0.391	2.38	130	71	5.1	1.0300	0.074
36	300	150	0.311	0.637	2.79	142	65	13.5	1.0243	0.177
37	308	150	0.217	0.830	2.81	170	106	16.0	1.0211	0.205
38	304	150	0.192	0.528	2.74	138	50	10.8	1.0271	0.138
39	218	150	0.222	0.321	2.67	136	42	3.9	1.0393	
40	242	185	0.199	0.562	2.13	162	104	15.1	1.0188	0.153
41	263	185	0.184	0.587	2.12	190	118	18.7	1.0197	0.196
42	226	185	0.174	0.423	2.44	164	69	10.6	1.0247	0.146
43	277	185	0.168	0.302	2.52	154	48	6.5	1.0313	0.026
44	152	185	0.193	0.366	2.27	176	174	11.8	1.0165	0.071
45	238	185	0.276	0.470	2.29	154	118	18.6	1.0196	0.227
46	190	188	0.151	0.252	2.04	124	58	7.7	1.0225	0.073
47	293	188	0.252	0.540	2.68	132	83	16.6	1.0196	0.163
48	290	188	0.191	0.398	3.01	120	55	5.6	1.0397	0.122
49	358	188	0.173	0.341	3.28	120	44	5.6	1.0361	0.018
50	228	188	0.201	0.362	2.84	124	50	4.6	1.0383	0.111
51	219	188	0.181	0.310	2.95	120	47	5.3	1.0383	0.054

* One day concentration test

tion test. There was a slight increase in the percentage of animals having increased blood pressure.

Eighty Per Cent Whole Liver Diet (Table 8) The volume of urine was within normal limits in 2 per cent of the rats. Rats with volume above normal were grouped as follows: from 5 to 10 cc, 35 per cent; from 10 to 15 cc, 39 per cent; from 15 to 20 cc, 21 per cent; and two rats excreted 20.7 and 22.1 cc, respectively.

With respect to the specific gravity of the urine, the rats were grouped as follows from 1 0100 to 1 0200, 43 per cent, from 1 0200 to 1 0300, 48 per cent, and from 1 0300 to 1 0400, 9 per cent. With respect to the urinary protein excreted, they were grouped as follows from 0 000 to 0 50 Gm, 60 per cent, from 0 50 to 0 100 Gm, 23 per cent, from 0 100 to 0 150 Gm, 13 per cent, and from 0 150 to 0 200 Gm, 4 per cent.

TABLE 8—*Observations on Partially Nephrectomized Animals Receiving 80 per Cent Whole Liver*

Rat	Weight, Gm	Duration of Experiment, Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty-Four Hour Urine Concentration Test		
			Surface Area ×100	Surface Area ×100	Surface Area ×100			Volume Cc	Specific Gravity	Albumin, Gm
1	144	14	0 130	0 166	2 05	120	126			
2	176	14	0 136	0 202	1 97	112				
3	128	20	0 136	0 205	2 36	124	78	8 7	1 0305	0 007*
4	120	27	0 151	0 216	2 44	120	166	8 7	1 0259	0 035*
5	106	27	0 153	0 266	2 61	124		7 5	1 0272	0 013*
6	133	27	0 146	0 264	2 40	122	160	8 5	1 0250	0 034*
7	190	27	0 143	0 343	2 27	120	116	15 0	1 0232	0 038*
8	106	27	0 130	0 326	2 21	126	110	7 6	1 0230	0 006*
9	120	27	0 141	0 284	2 38	124	105	11 5	1 0175	0 006*
10	164	31	0 150	0 354	2 34	112	180	9 0	1 0226	0 018*
11	188	31	0 145	0 277	2 08	130	133	9 5	1 0273	0 010*
12	164	31	0 158	0 227	2 13	126	197	15 6	1 0213	0 027*
13	152	31	0 157	0 210	1 96	116	176	12 0	1 0193	0 019*
14	168	31	0 150	0 339	2 12	118	196	16 7	1 0223	
15	168	32	0 141	0 278	2 03	126	117			
16	188	39	0 154	0 333	2 23	133	119	17 6	1 0239	0 046*
17	162	39		0 313	2 30	116		11 1	1 0251	0 035*
18	178	39	0 148	0 307	2 04	128	116	17 7	1 0222	0 030*
19	98	40	0 170	0 368	2 50	160	160	10 1	1 0222	0 039*
20	167	40	0 163	0 448	2 53	156	115	14 2	1 0241	0 146*
21	116	40	0 170	0 332	2 43	152	185	12 2	1 0234	0 059*
22	139	40	0 159	0 344	2 74	144	83	5 5	1 0333	0 011*
23	176	47	0 185	0 391	2 91	146	100	16 3	1 0218	
24	195	47	0 167	0 489	3 25	140	78	8 4	1 0252	
25	274	68	0 197	0 898	3 74	146	80	17 8	1 0224	0 123*
26	103	69	0 203	0 315	2 14	153	119	4 5	1 0105	0 009
27	187	69	0 198	0 523	2 63	148	123	14 2	1 0168	0 040
28	211	69	0 205	0 710	2 74	150	202	20 7	1 0150	0 083
29	227	72	0 248	0 905	2 61	194	156	13 0	1 0175	0 012
30	180	87	0 182	0 693	3 13	138	123	16 4	1 0169	0 103
31	122	91	0 175	0 374		168		7 6	1 0226	0 063
32	129	102	0 232	0 528		180	170	12 4	1 0176	0 051
33	300	113	0 229	0 527	2 78	153	74	16 4	1 0192	0 043
34	260	113	0 204	0 519	2 47	158	81	16 0	1 0174	0 038
35	185	116	0 203	0 514	2 62	156	132	12 8	1 0241	
36	255	117	0 202	0 639	2 41	146	149	13 8	1 0153	0 015
37	337	117	0 198	0 483	2 79	133	67	9 5	1 0262	0 030
38	130	120	0 166	0 253	2 53	140	161	10 7	1 0206	0 047
39	87	120	0 202	0 537	2 76	140	237	10 0	1 0191	0 102
40	172	120	0 194	0 582	2 78	132	222	14 0	1 0171	0 064
41	169	120	0 186	0 428	2 68	144	132	14 2	1 0189	0 044
42	345	126	0 229	0 640	3 09	130	127	18 6	1 0204	0 117
43	292	126	0 228	0 597	2 55	148	100	15 8	1 0202	0 103
44	121	150	0 192	0 375	1 93	122	193	8 7	1 0177	0 017
45	137	150	0 186	0 353	2 37	138	132			
46	138	150	0 160	0 402	2 37	120	134	9 9	1 0181	0 048
47	146	150	0 219	0 722	2 35	190	242	14 3	1 0157	0 038
48	200	150	0 182	0 433	2 28	124	107	13 4	1 0182	0 075
49	172	151	0 189	0 457	2 32	178	78	9 3	1 0195	
50	181	151	0 168	0 391	2 65	122	65	5 4	1 0353	
51	146	151	0 140	0 527	2 20	154	135	12 5	1 0174	0 061
52	230	153	0 183	0 440	2 58	120	92	8 6	1 0307	0 039
53	163	153	0 160	0 438	2 77	120		10 0	1 0261	0 080
54	130	153	0 188	0 321	2 69	124	98	14 1	1 0164	0 057
55	214	153	0 183	0 396	2 53	120	161	22 1	1 0162	
56	230	174	0 177	0 482	3 47	130	60	5 8	1 0386	0 057
57	310	174	0 204	1 010	3 10	128	198	13 3	1 0224	0 182
58	308	174	0 193	1 170	3 21	124	150	12 5	1 0271	0 232
59	248	200	0 206	0 795	3 26	168	157	13 0	1 0189	0 156
60	132	204	0 222	0 422	2 51	190		18 6	1 0134	0 022

* One day concentration test

There was a large number of animals (62 per cent) with normal blood pressure. This may be due to the larger percentage of younger animals studied in this group. The first hypertensive rat was seen on the fortieth day after operation. The hypertensive animals were grouped as follows: from 140 to 150 mm, 13 per cent, from 150 to 160 mm, 13 per cent, and from 160 to 194 mm, 12 per cent.

Seven per cent of the animals in this group had normal nonprotein nitrogen concentration. Those with retention were grouped as follows: from 75 to 100 mg, 19 per cent, from 100 to 150 mg, 39 per cent, from 150 to 200 mg, 28 per cent, and from 200 to 250 mg, 7 per cent.

The values of the $\frac{H W}{S A}$ ratio were increased in 24 per cent of the animals. The values of the $\frac{L W}{S A}$ ratio varied between 1.93 and 3.26 (average, 2.54). The values of the $\frac{K W}{S A}$ ratio varied between 0.166 and 1.17 (average, 0.453).

This diet caused a still further increase in the retention of nitrogen. The percentage of animals having polyuria during the concentration test was slightly greater than that of any of those receiving the preceding diets. The number of rats with hypertension within a given period after operation seemed to be smaller than in the groups receiving the diets containing smaller quantities of liver. There was a diminution in the amount of urinary protein excreted by these animals. The values of the $\frac{H W}{S A}$ ratio were smaller for the animals of this group than for those of the same age in the previously described dietary groups, particularly as concerned younger animals. Despite the comparatively high mortality and increased renal damage, the toxicity of the diet was not reflected in any striking effect on the blood pressure.

Eighty Per Cent Liver Residue (Table 9) Twenty-six per cent of this group had normal urinary volume. Those with increased volume were grouped as follows: from 5 to 10 cc, 34 per cent, from 10 to 15 cc, 26 per cent, from 15 to 20 cc, 10 per cent, and 2 rats excreted 227 and 231 cc, respectively. With respect to the specific gravity, the rats were grouped as follows: from 1.0100 to 1.0200, 15 per cent, from 1.0200 to 1.0300, 58 per cent, from 1.0300 to 1.0400, 21 per cent, and from 1.0400 to 1.0600, 6 per cent. The amount of urinary protein was less than that excreted by those receiving diets L 20, L 40 and L 60, as shown by the following grouping: from 0.000 to 0.05 Gm, 67 per cent, from 0.05 to 0.1 Gm, 10 per cent, from 0.1 to 0.2 Gm, 12 per cent, and from 0.2 to 0.25 Gm, 11 per cent.

An unusually large number had a blood pressure below 120 mm (27 per cent), and 58 per cent had a blood pressure between 120 and 140 mm, and 85 per cent of the total number had a blood pressure within normal limits. A slight increase was noted in 13 per cent, and 2 rats had blood pressures of 152 and 172 mm, respectively.

Normal nonprotein nitrogen concentration was seen in 23 per cent of the rats. Those with retention were grouped as follows: from 100 to 150 mg, 34 per cent, from 150 to 200 mg, 25 per cent, from 200 to 250 mg, 9 per cent, and from 250 to 300 mg, 9 per cent.

The values of the $\frac{H W}{S A}$ ratio were elevated in 17 per cent of the group. The values of the $\frac{L W}{S A}$ ratio varied between 1.87 and 3.18 (average, 2.42). The values of the $\frac{K W}{S A}$ ratio varied from 0.163 to 1.06 (average, 0.534).

The response to this diet was unexpected and difficult to explain. The large number of animals with retention of nitrogen, polyuria and lowered specific gravity was evidence of an appreciable loss of renal function. However, despite this damage, few animals showed excessive

TABLE 9—*Observations on Partially Nephrectomized Animals Receiving 80 per Cent Liver Residue*

Rat	Weight, Gm	Duration of Experiment, Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty-Four Hour Urine Concentration Test		
			Surface Area ×100	Surface Area ×100	Surface Area ×100			Volume Cc	Specific Gravity	Albumin, Gm
1	181	30	0.162	0.396	2.60	124	121	13.8	1.0221	0.026
2	124	30	0.150	0.311	2.60	122	112	4.2	1.0324	
3	80	30	0.147	0.253	1.94	104		2.7	1.0354	
4	159	41	0.141	0.300	2.16	116		11.8	1.0236	0.034
5	170	41	0.166	0.288	2.23	110	132	9.7	1.0275	0.018
6	148	41	0.151	0.281	2.30	118		4.0	1.0515	
7	146	41	0.165	0.343	1.82	124	200	13.2	1.0299	0.013
8	160	66	0.151	0.335	2.09	120	120	8.0	1.0253	0.008
9	122	66	0.140	0.386	2.01	130	125	5.0	1.0303	
10	124	66	0.144	0.366	1.87	148	161	4.0	1.0286	
11	136	73	0.153	0.317	2.24	123	208	5.8	1.0254	
12	133	73	0.141	0.287	2.21	116	138	2.2	1.0354	
13	100	73	0.132	0.163	2.10	126	143	2.1	1.0344	
14	176	73	0.147	0.289	2.31	108	114	4.4	1.0342	
15	161	95	0.161	0.356	2.41	136	58	7.0	1.0311	0.011
16	132	95	0.149	0.400	1.97	130	67	3.7	1.0310	
17	157	95	0.154	0.435	2.38	144	66	8.5	1.0251	0.010
18	158	95	0.146	0.364	2.35	138	46	6.7	1.0293	0.011
19	144	95	0.161	0.503	2.19	124	96	9.0	1.0219	0.010
20	215	96	0.183	0.508		130	135	13.0	1.0259	0.091
21	180	105	0.226	0.535		136	160	16.0	1.0247	0.001
22	248	112	0.183	0.421	2.78	152	55	9.2	1.0282	
23	238	120	0.227	0.990	2.74	142	270	22.7	1.0175	0.168
24	336	120	0.184	0.648	3.18	126	106	9.2	1.0282	0.034
25	218	125	0.255	1.000	2.76	172	245	15.0	1.0175	0.192
26	235	125	0.267	0.945	2.56	130	182	14.5	1.0200	0.086
27	147	128	0.172	0.402		110	127	4.1	1.0326	
28	174	128	0.191	0.532	2.34	104	163	9.2	1.0234	0.017
29	282	149	0.234	0.915	2.68	148	227	23.1	1.0152	0.219
30	242	149	0.184	0.628	2.44	130	114	14.5	1.0197	0.042
31	186	154	0.199	0.894		134	183	11.9	1.0202	0.120
32	194	163	0.210	0.760	2.79	132	163	11.7	1.0212	0.206
33	240	163	0.186	0.672	2.63	132		9.1	1.0239	0.068
34	206	163	0.247	1.050	2.40	140	262	19.5	1.0152	0.143
35	160	169	0.195	0.990	2.13	126	288	17.2	1.0127	0.024
36	148	175	0.168	0.492	2.45	122	95	3.5	1.0437	
37	236	182	0.176	0.448	2.80	148	64	4.4	1.0466	0.000
38	250	182	0.195	0.965	2.81	134	148	14.0	1.0211	0.212
39	214	183	0.187	0.545	3.48	122	59	4.6	1.0322	0.078
40	152	194	0.194	0.557	2.30	120	152	15.3	1.0187	0.011
41	136	194	0.188	0.670	2.08	132	193	9.7	1.0241	0.038
42	136	195	0.217	0.902	1.88	112	282			
43	118	216	0.181	0.493	2.30	118	180	7.6	1.0236	0.013
44	134	226	0.157	0.344	2.27	116	158	5.6	1.0272	
45	152	226	0.169	0.457	2.84	134	154	10.8	1.0232	0.046
46	208	226	0.180	0.463	2.44	122	106	11.8	1.0236	0.028
47	246	226	0.185	0.543	2.80	128	149	12.3	1.0274	0.040
48	170	226	0.172	0.538	2.69	132	99	9.7	1.0245	0.083

excretion of protein or hypertension. It should be pointed out that although this diet was the richest in nitrogen content, the mortality rate was not so great as that of the animals fed the diets containing whole liver with a much smaller concentration of nitrogen.

Diet Rich in the Water-Soluble Constituents of Liver (Table 10). The urinary volume was normal in 22 per cent of the animals. Those with increased volume were grouped as follows: from 5 to 10 cc, 39 per cent; from 10 to 15 cc, 37 per cent; and two rats excreted 19.2 and 20.6 cc, respectively. With respect

to the specific gravity, the rats were grouped as follows from 1 0100 to 1 0200, 17 per cent, from 1 0200 to 1 0300, 59 per cent, from 1 0300 to 1 0400, 22 per cent, and one rat had a specific gravity of 1 0410 With respect to the amount of urinary protein excreted, they were grouped as follows from 0 000 to 0 50 Gm, 27 per cent, from 0 05 to 0 1 Gm, 30 per cent, from 0 1 to 0 15 Gm, 20 per cent, from 0 150 to 0 2 Gm, 17 per cent, and two rats excreted 0 214 and 0 216 Gm, respectively

TABLE 10—*Observations on Partially Nephrectomized Animals Receiving a Diet Rich in Aqueous Liver Extract*

Rat	Weight, Gm	Duration of Experiment, Days	Heart Weight	Kidney Weight	Liver Weight	Blood Pressure, Mm	Nonprotein Nitrogen, Mg per 100 Cc	Twenty-Four Hour Urine Concentration Test		
			Surface Area ×100	Surface Area ×100	Surface Area ×100			Volume Cc	Specific Gravity	Albumin, Gm
1	134	15	0 145	0 229	1 99	126	85	3 8	1 0300	
2	180	15	0 157	0 260	2 45	128	87	6 4	1 0263	
3	165	15	0 155	0 302	2 33	124	111	8 7	1 0228	
4	165	15	0 158	0 255	2 46	126		4 4	1 0232	
5	222	28	0 218	0 331	2 70	152	77	11 0	1 0255	0 082
6	157	28	0 210	0 283	2 33	116	99	6 7	1 0295	
7	166	28	0 176	0 330	2 71	114	92	5 0	1 0289	0 029
8	172	23	0 186	0 301	2 53	120	65			
9	161	39	0 161	0 271	2 43	126	66	5 8	1 0294	0 023
10	170	39	0 163	0 256	2 48	123	55	5 2	1 0305	0 004
11	184	39	0 178	0 244	2 32	120	64	7 0	1 0273	0 037
12	169	39	0 178	0 258	2 44	124	46	5 6	1 0231	0 016
13	240	85	0 203	0 396	2 44	122	95	11 2	1 0300	0 142
14	181	85	0 193	0 423	2 91	124	86	10 4	1 0237	0 094
15	164	112	0 186	0 296	2 63	123	92	10 3	1 0209	0 149
16	140	112	0 222	0 348	2 34	170	111	14 0	1 0193	0 122
17	162	112	0 183	0 331	2 46	170	101	11 5	1 0181	0 135
18	293	124	0 234	0 410	2 22	168	80	11 6	1 0260	0 099
19	280	124	0 238	0 391	2 44	176	76	19 2	1 0188	0 153
20	176	124	0 253	0 396	2 28	184	116	14 8	1 0176	0 092
21	237	125	0 219	0 350	2 28	152	45	10 4	1 0323	0 144
22	367	125	0 226	0 360	2 91	140	44	10 7	1 0312	0 109
23	300	131	0 213	0 321	1 90	130	57	8 6	1 0238	0 053
24	276	131	0 180	0 263	1 87	144		4 1	1 0273	
25	230	131	0 176	0 334	2 10	142	47	4 6	1 0334	
26	215	142	0 218	0 315	2 12	138	83	12 8	1 0189	0 092
27	179	142	0 196	0 308	2 53		56	6 9	1 0292	0 036
28	153	142	0 230	0 380	2 71	160	95	11 4	1 0191	0 198
29	274	147	0 175	0 334	2 07	118	37	3 1	1 0410	
30	322	147	0 174	0 369	2 27	135	53	5 9	1 0314	0 040
31	236	147	0 169	0 392	2 36	146	47	4 2	1 0352	
32	214	147	0 170	0 324	1 72	114	51	4 4	1 0267	0 002
33	226	147	0 155	0 264	1 90	123	46	4 1	1 0263	
34	300	157	0 223	0 481	2 44	134	67	8 0	1 0232	
35	211	164	0 201	0 390	3 70	124	104	8 9	1 0212	0 063
36	185	164	0 229	0 383	2 71	190	129	10 0	1 0238	0 172
37	188	164	0 226	0 320	2 85	158	112	12 9	1 0190	0 194
38	154	176	0 163	0 275	2 03	120	80	7 9	1 0227	0 031
39	232	176	0 167	0 392	2 35	162	59	5 1	1 0305	0 075
40	224	176	0 196	0 392	2 53	144	84	20 6	1 0225	0 214
41	265	176	0 217	0 333	2 25	164	73	12 0	1 0225	0 163
42	200	191	0 183	0 407	3 60	154	55	9 4	1 0231	0 216

Fifty-six per cent of this group had blood pressures within normal limits Those with elevated blood pressures were grouped as follows from 140 to 150 mm, 12 per cent, from 150 to 160 mm, 10 per cent, from 160 to 180 mm, 17 per cent, and from 180 to 200 mm, 5 per cent

Normal nonprotein nitrogen concentrations were seen in 17 per cent of the animals Those with retention were grouped as follows from 50 to 100 mg, 63 per cent, and from 100 to 150 mg, 17 per cent

The values of the $\frac{H W}{S A}$ ratio were elevated in 41 per cent The values of the $\frac{L W}{S A}$ ratio varied between 1 72 and 3 70 (average, 2 41) Those of the $\frac{K W}{S A}$ ratio ranged between 0 229 and 0 491 (average, 0 336)

This diet caused the greatest mortality among the experimental animals. Despite the apparent toxicity, the concentration test did not indicate severe renal insufficiency, nor was the albuminuria particularly marked, and the retention of nitrogen was only moderately elevated. The frequency and the degree of hypertension were no more marked than in animals fed moderate or large quantities of whole liver.

ANALYSIS OF OBSERVATIONS

If graded amounts of a nephrotoxic material are added to the diet of partially nephrectomized rats, the effects should be manifested to a certain degree in the volume of urine, the ability to concentrate urine, the amount of protein in the urine, the blood pressure, azotemia and

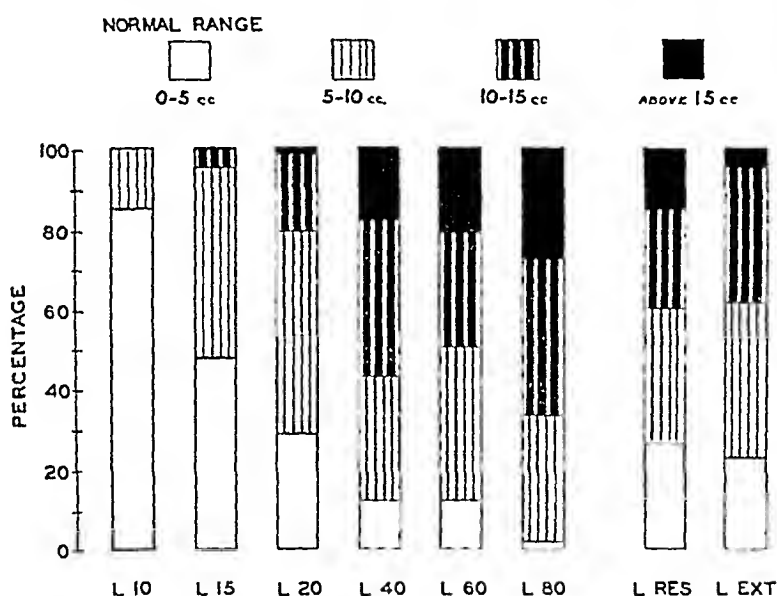


Chart 1—The relation of the urinary volume to diet in partially nephrectomized rats

the weights of the heart, liver and kidney. The effects of the various diets containing liver on each of these functions and on the organs studied are discussed.

Urine Concentration Test—The ability of the organism to retain fluid during a period of abstinence from food and water has been utilized as a test of renal function. Intact and unilaterally nephrectomized animals secrete small amounts of concentrated urine. Chart 1 shows in diagrammatic form the effects of the various diets on the urinary volume of partially nephrectomized animals. The progressive increase in the incidence and the degree of polyuria with graded increments of whole liver is striking. Mild polyuria in 15 per cent of the rats receiving diet L 10 offers a strong contrast to the 98 per cent which secreted more than the normal amount when receiving diet L 80. The volume

of urine excreted by the animals receiving the L Res and L Ext diets was between those obtained from groups receiving L 20 and L 40 diets

Chart 2 shows the effect of the same diets on the specific gravity of the urine. It will be seen that the ability to concentrate in general varies inversely with the percentage of whole liver in the diet. The regular increase in the percentage of animals (represented by solid black) with hyposthenuria is noteworthy. In only a small number of animals receiving the L Res and L Ext diets was the concentration normal.

It is interesting that few (18 per cent) receiving the L 10 diet had normal concentration whereas most (85 per cent) receiving the same diet excreted a normal amount. The volume of urine excreted by many

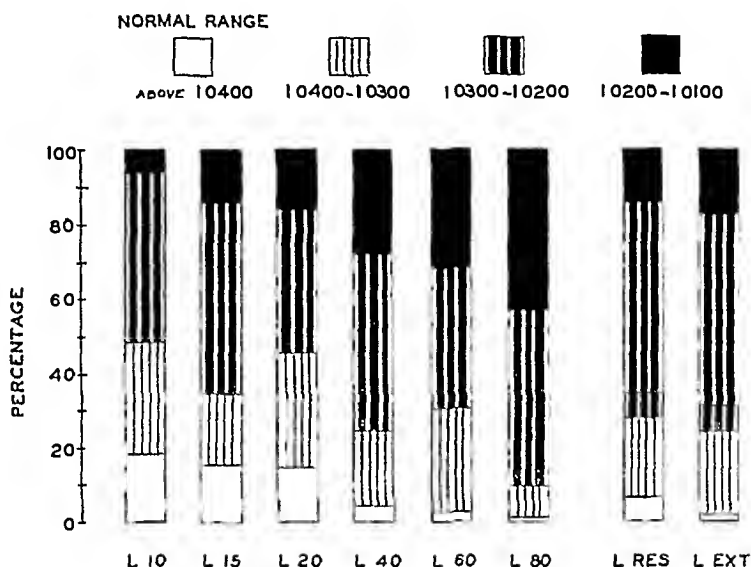


Chart 2—The relation of specific gravity to diet in partially nephrectomized rats

of these animals, without food and water, exceeded their blood volume (about 20 cc in a rat weighing 300 Gm.)

Albuminuria—Chart 3 summarizes the effects of the diets on the excretion of protein. Freedom from abnormal albuminuria in the animals receiving the L 10 diet was outstanding, as was the fact that here again the animals fed the L 80 and L Res diets excreted less than the groups fed diets L 60, L 40 and L 20. The most striking albuminuria was seen in the diet group receiving L 40, with those receiving diets L 20, L 60 and L Ext having about an equal amount. There were marked variations in the amount of protein excreted by the individual members of each group. This seemed independent of the time elapsed after operation and the volume of urine excreted.

Hypertension—Chart 4 summarizes the effects of the diets on the blood pressure. The absence of significant hypertension (over 160 mm) in those receiving the L Res diet was remarkable. This diet contained

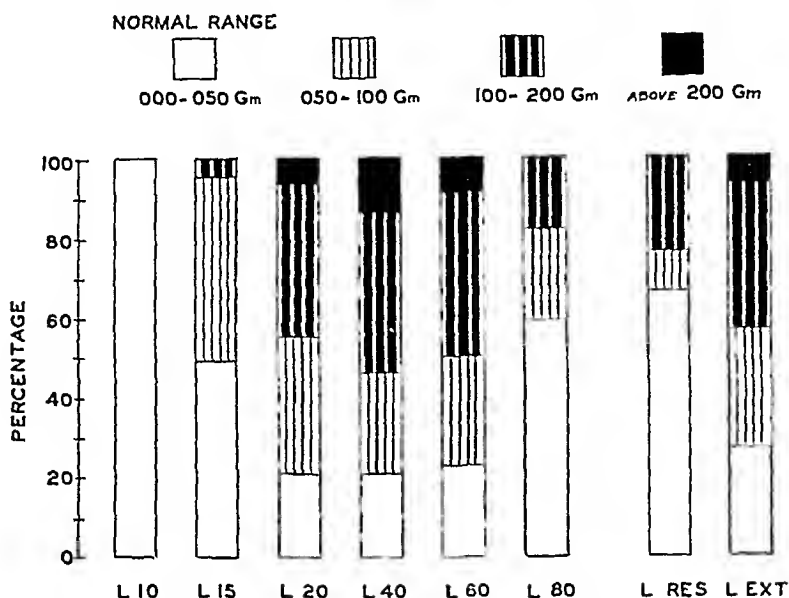


Chart 3—The relation of urinary protein to diet in partially nephrectomized rats

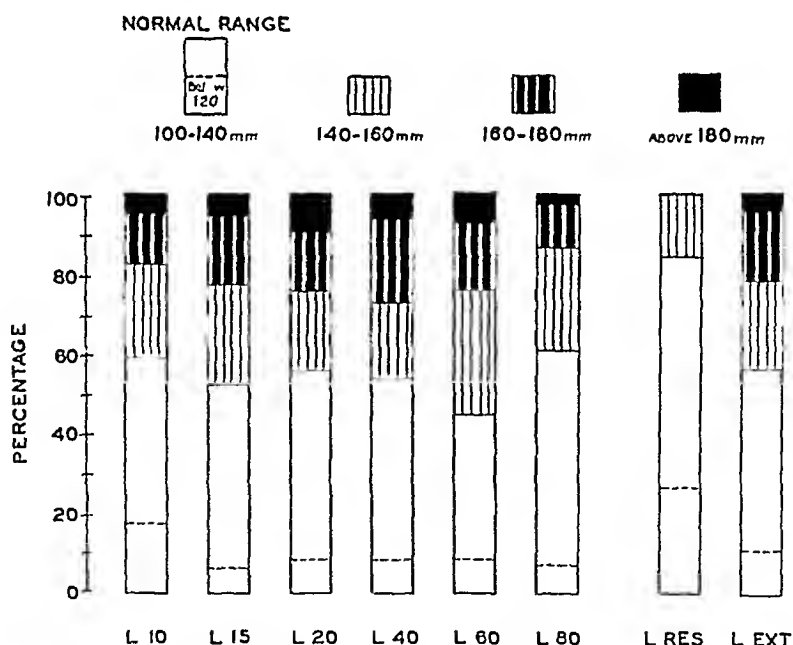


Chart 4—The relation of blood pressure to diet in partially nephrectomized rats

the highest percentage of protein, but it was free from the water-soluble liver substances. Strangely enough, the next lowest incidence of hypertension was in the group receiving diet L 80, which was the group with the next highest concentration of protein and a large content of the water-soluble liver constituents. This was more remark-

able when compared with the group receiving diet L 60, which had the largest percentage of animals with hypertension. The differences between the other groups were not significant.

It is possible that the difference in time elapsed between the operation and the blood pressure readings in the different groups explains some of the apparent inconsistencies. It was found that hypertension did not appear in the group receiving diet L 10 until the hundred and fifty-second day after the operation, whereas in the other groups (except in that receiving the L Res diet) it was noted during the first sixty days. Owing to the fact that the number of animals killed at definite intervals was not the same, no comparison can be made between the various groups. This is further complicated by the fact that daily variations for

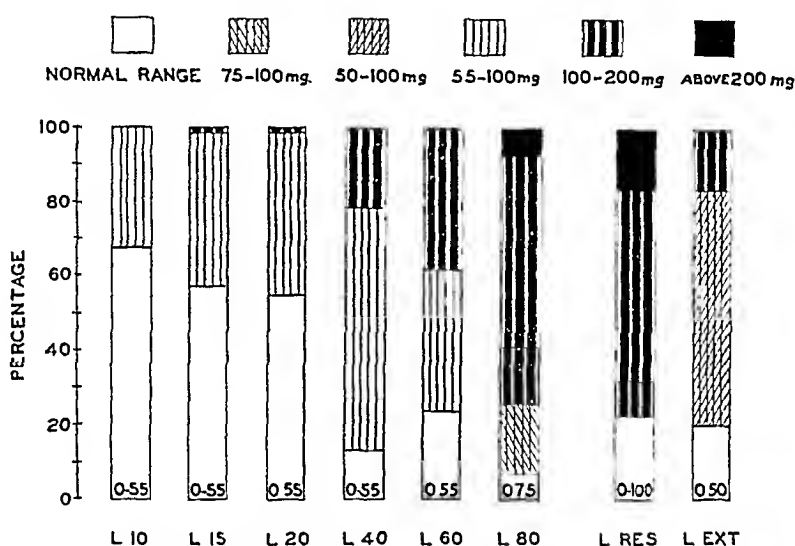


Chart 5—The relation of azotemia to diet in partially nephrectomized rats. The normal range refers to values obtained in comparable control groups.

each rat could not be obtained, because only one reading for terminal blood pressure for each rat was possible.

Azotemia—Chart 5 demonstrates the effect of the diets on the retention of nonprotein nitrogen. Significant retention of nitrogen was not noted in the groups receiving the L 10, L 15 and L 20 diets. Additional increments of whole liver were followed by an increased incidence and degree of azotemia. The most marked retention was noted in the group receiving diet L Res. The rats receiving the L Ext diet had a retention about equal to that of the group receiving diet L 40. It was impossible to correlate the degree of retention of nitrogen with the health, renal function, albuminuria, blood pressure or pathologic changes (K'ang).

Heart—In the majority of the animals the relationship between hypertension and the weight of the ventricles was the same as that found by Chanutin and Ferris¹ and Chanutin and Barksdale¹⁰. Most of the discrepancies noted were in the younger animals shortly after operation. The effect of diet on the weight of the ventricles seemed to be indirect, and dependent on the presence or absence of hypertension.

Liver—The increased values of the $\frac{LW}{SA}$ ratio in the control animals receiving the L 40, L 60 and L 80 diets were probably due to the high ingestion of protein and the deposition of fat from the relatively large amounts of cholesterol in the whole dried liver. Chemical analyses of a few representative animals from the groups receiving the L 40, L 60 and L 80 diets showed abnormally large amounts of fat. This conforms with the findings of Blatherwick and his associates¹¹ of increased deposition of fat in the liver after the ingestion of diets rich in whole dried liver.

In striking contrast was the absence of this fatty change in the livers of the control group of animals receiving the L Res diet (highest in protein), though the values of the $\frac{LW}{SA}$ ratio were just as high as in the group receiving the L 60 diet. Since the animals in this group were young at the beginning of the experiment, these observations are in accord with those of MacKay, MacKay and Addis,¹² who observed an increased weight of the liver in young rats fed a diet high in protein (casein).

The $\frac{LW}{SA}$ ratios of corresponding partially nephrectomized animals were of smaller value than those of the controls. It is difficult to attribute the smaller livers to renal insufficiency, particularly since the small livers of the animals receiving the diet containing whole liver were also fatty. The L Ext diet produced no significant change.

Kidney—Chart 6 shows the effect of the diets on the $\frac{KW}{SA}$ ratio in the controls and the partially nephrectomized rats, the value of the ratio increasing with the nitrogen content of the diets containing whole liver and liver residue. Determinations of the total solids on a few of the kidney stumps indicated that a part, at least, of the increased weight was due to increased renal substance, a variable part being due to increased water.

10 Chanutin, Alfred, and Barksdale, E. E. Experimental Renal Insufficiency Produced by Partial Nephrectomy. II. Relationship of Left Ventricular Hypertrophy, the Width of the Cardiac Muscle Fiber and Hypertension in the Rat, Arch Int Med **52** 739 (Nov) 1933.

11 Blatherwick, N. R., Medlar, E. M., Bradshaw, Phoebe J., Post, Anna L., and Sawyer, Susan D. J Biol Chem **103** 93, 1933.

12 MacKay, E. M., MacKay, L. L., and Addis, T. Am J Physiol **86** 466, 1928.

MacKay and MacKay¹³ showed that predictable increases in the weight of the kidney follow increases in protein in the diet, but that the increases could be materially lessened by adding enough vitamin B complex to the diet (MacKay¹⁴). Investigation showed that diets L 20 to L 80 contained adequate vitamin B complex to permit the successful reproduction of large healthy litters in the control animals, whereas diets L 15 and L 10 did not. The hypertrophy of the kidneys of animals receiving the L Ext diet was approximately what was to be expected from the nitrogen content. In these experiments the vitamin B complex, though sufficient to permit successful reproduction, did not prevent the progressive enlargement of the kidneys of the animals fed increasing amounts of whole liver.

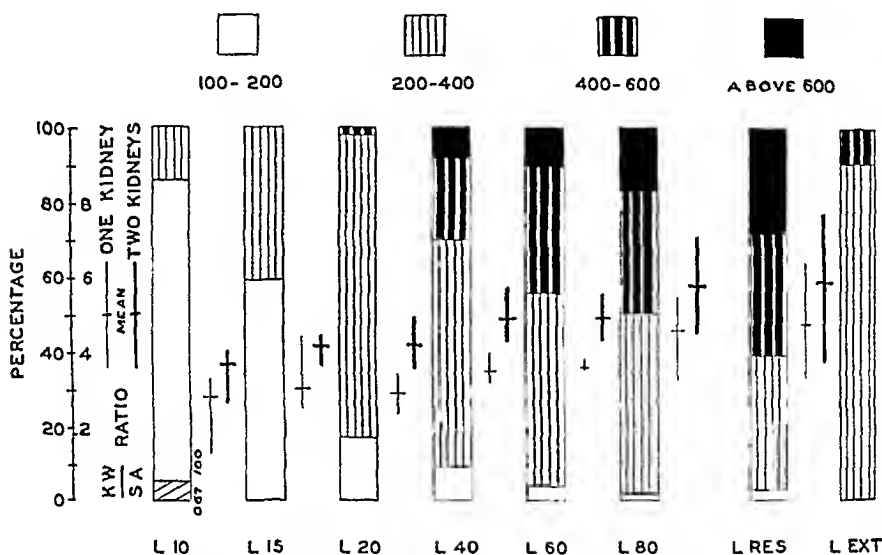


Chart 6—The relation of $\frac{KW}{SA}$ ratio to diet in control and partially nephrectomized rats

K'ang⁹ found that the pathologic changes in the kidney stumps became more severe as the amount of whole dried liver in the diet was increased. The diet containing liver extract produced the most severe renal damage, and the diet containing liver residue the least.

Hemoglobin—Hemoglobin determinations were not included in the tables because there was little difference among the animals fed the various diets. Whole liver or liver extract did not cause an excessive formation of hemoglobin, nor did it prevent moderate anemia in many. In a few rats acutely ill the anemia was rather severe. It was interesting that anemia could develop in animals receiving these liver diets, which were rich in the factors for preventing anemia.

13 MacKay, E. M., and MacKay, L. L. *J. Nutrition* 3: 375, 1931

14 MacKay, E. M. *Am. J. Physiol.* 106: 571, 1933

The Acute Condition in Partially Nephrectomized Rats—Many animals became acutely ill within forty-eight hours after the second operation, when the intact kidney was removed. The course resembled that of animals after total nephrectomy. There was usual retention of nitrogen without edema and very low blood pressure.

Some animals became acutely ill after the first postoperative month, with listlessness, tetanic convulsions or quadrilateral paralysis with hypertension. They died in a few hours, some in coma, others in convulsions.

COMMENT

The relation between renal damage and hypertension is still unsolved. Among clinicians there is a difference of opinion as to whether renal insufficiency is a primary cause of hypertension. Following reduction of the functional renal substance in experimental animals pathologic changes occur which are accompanied by hypertension, cardiac hypertrophy, an increased flow of dilute urine, retention of nitrogen and the elimination of albumin and casts. In many respects this syndrome is analogous to certain types of renal involvement in man. The production of experimental hypertension is of importance, since it shows that hypertension can be secondary to renal damage.

In his discussion of renal insufficiency, Fishberg¹⁵ stated

The height to which blood urea rises as a result of renal failure depends on various factors, notably the severity and duration of impairment of renal function, the fluid intake, the amount of protein in the diet, the rate of katabolism of protein in the body and perhaps the functional condition of the liver, the organ which forms urea. There are no definite levels at which uremic symptoms set in or death occurs. Uremic coma occurs on rare occasions with less than 100 mg per cent of urea in the blood, particularly if the protein content of the diet has been rigidly restricted and large quantities of carbohydrates successfully administered.

It is of interest to note that in partially nephrectomized rats, as in human beings with damaged kidneys, there is no exact relationship between the retention of nitrogen and morbid symptoms. Furthermore, it should be noted that in such rats the degree of retention is related to the nitrogen content of the diet.

Keutmann and McCann¹⁶ reported that patients with chronic Bright's disease appeared to show a general improvement after ingesting large amounts of protein. These observations were conducted for a relatively short time, and the highest amounts of protein ingested comprised about 25 per cent of the total amount of energy of the diet. This

¹⁵ Fishberg, A. M. *Hypertension and Nephritis*, ed. 3, Philadelphia, Lea & Febiger, 1934, p. 24.

¹⁶ Keutmann, E. H., and McCann, W. S. *J. Clin. Investigation* **11** 973, 1932.

maximum intake of protein would correspond roughly to the experimental diet containing 40 per cent whole liver, in respect to the caloric value of the protein present. The larger concentrations of whole liver, liver residue and liver extract fed to rats probably could not be tolerated by man for any length of time.

It has been demonstrated in these experiments that a diet low in protein (L 10) will delay, but will not prevent, the appearance of hypertension, in addition, there is little retention of nitrogen, albuminuria and polyuria. These findings may serve as an experimental confirmation for the use of diets low in protein in renal damage or hypertension in man. Relatively small amounts of protein in the diets that were considered to be normal for intact rats (L 15 and L 20) were responsible for an increased excretion of dilute urine containing more urinary protein and for the early appearance of hypertension. In contrast to these observations it was seen that the experimental animals ingesting a diet extremely rich in protein (L Res) showed no marked effect on the blood pressure, albuminuria or renal changes despite the increased excretion of dilute urine and the marked retention.

The conflicting results seen in clinical observations have been encountered in the present experiments. An effort to find a common factor which could be correlated with the various experimental findings has not been successful. Moderate and severe hypertension were encountered with and without marked renal insufficiency. Furthermore, the degree of hypertension was not dependent on the extent of renal damage as judged by the concentration test, retention of nitrogen or pathologic changes. The amount of urinary protein excreted was not predictable from the quantity of urine excreted. Apparently renal insufficiency alone cannot be the direct cause of the findings noted in this study.

SUMMARY

The effect of feeding diets containing varying percentages (10, 15, 20, 40, 60 and 80) of whole dried liver, liver residue (80) and aqueous liver extract to intact, unilaterally nephrectomized and partially nephrectomized rats has been studied.

The ingestion of these diets by intact and unilaterally nephrectomized animals was followed by enlargement of the kidneys which was roughly proportional to the nitrogen content of the diet, the liver was similarly increased in weight owing to the deposition of fat and the effect of ingestion of an increased amount of protein, the azotemia was more marked in those animals receiving the diets containing more liver, the renal function was unaffected. An appreciable number of unilaterally nephrectomized rats had slightly increased blood pressure.

The syndrome obtained in the partially nephrectomized rats was affected by the percentage of whole liver and liver fractions in the diet in the following manner

1 A progressively increased quantity of dilute urine was excreted as the content of whole liver was raised. Neither the administration of liver residue nor of liver extract caused marked changes in the volume or specific gravity of the urine. The amount of urinary protein excreted had no relation to the volume of urine.

2 Hypertension was delayed in the rats receiving the diet that is 10 per cent whole liver. The addition of a small amount of liver had a definite effect on the early appearance of hypertension. The rats receiving the diet containing liver residue showed practically no hypertension despite evidence of renal damage.

The degree of azotemia appeared to depend on the amount of nitrogen in the diet.

In the older animals there was a relationship between the blood pressure and the $\frac{H W}{S A}$ ratio. Discrepancies in this relationship were noted in the younger animals. The values of the $\frac{L W}{S A}$ ratio were smaller than those for the corresponding controls. The values of the $\frac{K W}{S A}$ ratio were extremely variable, but were roughly proportional to the amount of nitrogen in the diet.

In partially nephrectomized animals, the degree of renal insufficiency, albuminuria, retention of nitrogen and, to a certain extent, the occurrence and degree of hypertension were found to vary according to the diet fed. The factors responsible for the acute illness, hypertrophy of the kidney, polyuria and hypertension are still unknown and poorly understood.

THERAPEUTIC EFFECT OF TOTAL ABLATION OF NORMAL THYROID ON CONGESTIVE HEART FAILURE AND ANGINA PECTORIS

VIII RELATIONSHIP BETWEEN SERUM CHOLESTEROL VALUES, BASAL METABOLIC RATE AND CLINICAL ASPECTS OF HYPOTHYROIDISM

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M C VOLK, A B

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The relationships between the serum cholesterol concentration, the basal metabolic rate and the clinical aspects of hypothyroidism induced by total removal of the normal thyroid gland in patients with chronic intractable heart disease have been studied and are reported in this communication¹ By means of preoperative measurements and measurements at appropriate intervals after total thyroidectomy, it has been possible to observe the development of changes in the serum cholesterol values and the basal metabolic rate as hypothyroidism developed in these patients who before operation had no thyroid disease The development of untoward symptoms of myxedema necessitated the administration of minimal amounts of thyroid substance to many of the patients, thus affording an opportunity to study the effect of this medication on the aforementioned relationships

Mason, Hunt and Hurxthal² reviewed the literature up to 1930 on the relationship of blood cholesterol concentration to the activity of the thyroid gland in thyroid disease Further studies by these authors strengthen the observation that the plasma cholesterol is increased in

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1 The operations were performed by Dr David D Berlin and Dr Charles G Mixer

2 Mason, R L, Hunt, H M, and Hurxthal, L M Blood Cholesterol Values in Hyperthyroidism and Hypothyroidism Their Significance, New England J Med **203** 1273, 1930

myxedema and, less regularly, decreased in thyrotoxicosis. No exact quantitative relationship, however, was found between the plasma cholesterol concentration and the basal metabolic rate. When, by appropriate therapeutic procedures, the basal metabolic rate in myxedema and hyperthyroidism is rendered normal, the abnormal plasma cholesterol concentration likewise returns to normal.³ The plasma cholesterol concentration, therefore, has been employed as an aid in the diagnosis and treatment of thyroid disease.⁴ Especially in cases in which reliable measurements of basal metabolic rates cannot be obtained, the plasma cholesterol concentration has been found to be of distinct value.^{3a}

METHODS

Blood for cholesterol measurements was drawn from the antecubital vein, with minimal stasis, after a fast of fourteen hours or more. Measurements of serum cholesterol were made in duplicate by the method of Myers and Wardell,⁵ using the apparatus for continuous extraction described by Ling.⁶ The averages of the duplicate measurements, which checked within 5 per cent, have been reported. The high limit accepted for normal serum cholesterol values is generally about 230 mg per hundred cubic centimeters.

Measurements of the basal metabolic rate were made in duplicate with a Collins-Benedict-Roth apparatus, and results calculated according to the Aub-DuBois normal standards.⁷ The averages of duplicate analyses, which checked within 5 per cent, are reported. The preoperative values represent the average of several such measurements on different days. Preoperative measurements and those taken during the first two postoperative weeks were made while the patient was hospitalized. The majority of the basal metabolic rates after the first two weeks were measured when the patient came to the laboratory from his home and rested quietly in bed for from one-half to one hour. Although the latter condition is not as ideal as when patients stay overnight in the hospital, it is felt the measurements of the basal metabolic rate given here are reliable.

When weakness of the legs, drowsiness, emotional irritability or puffiness of the face developed, thyroid substance was administered in appropriate amounts to alleviate these untoward symptoms of myxedema without raising the basal metabolic rate sufficiently to place an undue burden on the heart. The amounts of

3 (a) Bronstein, I. P. Studies in Cretinism and Hypothyroidism in Childhood. I. Blood Cholesterol, *J. A. M. A.* **100** 1661 (May 27) 1933. (b) Hurxthal, L. M. Blood Cholesterol in Thyroid Disease. II. Effect of Treatment, *Arch. Int. Med.* **52** 86 (July) 1933. (c) Levy, M., and Levy, M. (Mme). Le traitement de l'hypercholestérolémie par la thyroxine, *Bull. Acad. de méd., Paris* **105** 666, 1931. (d) Mason, Hunt and Hurxthal.²

4 Mason, Hunt and Hurxthal.² Bronstein.^{3a} Hurxthal.^{3b}

5 Myers, V. C., and Wardell, E. L. The Colorimetric Estimation of Cholesterol in Blood, with a Note on the Estimation of Coprosterol in Feces, *J. Biol. Chem.* **36** 147, 1918.

6 Ling, S. M. The Determination of Cholesterol in Small Amounts of Blood, *J. Biol. Chem.* **76** 361, 1928.

7 Aub, J. C., and Du Bois, E. F. Clinical Calorimetry. XIX. The Basal Metabolism of Old Men, *Arch. Int. Med.* **19** 823 (May) 1917.

thyroid substance administered were so adjusted as to maintain the patient in a hypothyroid state, as evidenced by dry skin, increased sensitivity to cold and a low basal metabolic rate

RESULTS

Simultaneous measurements of the serum cholesterol concentration and the basal metabolic rate were made in twenty-nine patients before and at frequent intervals after complete thyroidectomy, in eighteen other patients the same measurements were made at postoperative intervals only (table). The ages of the subjects studied varied from 14 to 66 years, sixteen were female and thirty-one male. Twenty-eight patients suffered from congestive heart failure at the time of or just prior to operation, fourteen had angina pectoris and five had no cardiac involvement.

Relationships Between Serum Cholesterol Value and Basal Metabolic Rate Before Total Thyroidectomy—The preoperative serum cholesterol values ranged between 92 and 298 mg per hundred cubic centimeters, and the basal metabolic rates in the same twenty-nine cases varied between plus 13 and minus 24 per cent (table). Seven subjects had preoperative serum cholesterol values above 230 mg per hundred cubic centimeters. Four of these had coexisting diseases, such as diabetes (cases 23, 25 and 27) and Paget's disease (case 28), which may increase the serum cholesterol concentration.⁸ The other three patients with high preoperative serum cholesterol values had basal metabolic rates between minus 14 and minus 23 per cent (cases 24, 26 and 29). Although one cannot detect any further significant correlation between the basal metabolic rate and the serum cholesterol concentration in the subjects of this study, a tendency toward such a correlation has been observed by studying a much larger group of subjects with no disease of the thyroid gland.⁹

Relationship Between Serum Cholesterol Concentration and Basal Metabolic Rate in Untreated Hypothyroidism After Total Thyroidectomy—As the basal metabolic rate decreased, the serum cholesterol concentration increased, following total ablation of the thyroid gland (table). In a given patient the increase in serum cholesterol concentration bore no precise quantitative relation to the decrease in basal metabolic rate. The highest cholesterol values obtained were, however, found in six of the eight patients whose basal metabolic rates were decreased to minus 35 per cent or lower. In one patient (case 39) the basal metabolic rate had not shown a significant decrease by the end

8 Lasch, F. Biochemische Untersuchungen bei Ostitis deformans Paget, Wien Arch f inn Med **21** 159, 1931.

9 Volk, M. C., Abrams, M. I., and Gilligan, D. R. The Relationship Between Serum Cholesterol and Basal Metabolism in Subjects with no Thyroid Disease, With Particular Reference to Subjects with Low Basal Metabolic Rates, to be published.

of the second postoperative month. The serum cholesterol concentration at this time, however, was increased to 368 mg per hundred cubic centimeters, and clinical evidences of hypothyroidism were present.

A change in both the basal metabolic rate and the serum cholesterol concentration was usually observed as early as the first postoperative week. By the end of the first postoperative month the basal metabolic rate had usually decreased to approximately its lowest value, whereas the serum cholesterol concentration tended to increase steadily during the next few months (figure). Thus, in a series of patients who were not receiving thyroid medication, the average basal metabolic rate fluctuated between the narrow limits of from 25 to 29 per cent below the preoperative average during the period from one to six months after operation, whereas the average serum cholesterol value gradually increased during this period from 88 to 153 mg per hundred cubic centimeters above the preoperative average.

Relationship of the Serum Cholesterol and the Basal Metabolic Rate to Untreated Signs and Symptoms of Myxedema After Total Thyroidectomy—After varying periods of time some of the signs and symptoms of myxedema developed in every patient following total thyroidectomy. By the end of the first postoperative month most of the patients showed mild clinical signs and symptoms, such as dry skin, slight pallor and sensitivity to cold. After the second postoperative month more serious symptoms of myxedema developed in many of the patients, such as weakness of the extremities, drowsiness, emotional irritability and transient puffiness of the face, hands and feet. The serious symptoms were relieved by the administration of small doses of thyroid substance.

When the first clinical signs and symptoms of myxedema appeared, the basal metabolic rate was usually reduced to minus 20 per cent or lower, and the serum cholesterol value was, with few exceptions, above 200 mg per hundred cubic centimeters (table). The untoward symptoms of myxedema were usually not observed until the basal metabolic rate had remained at levels of approximately minus 30 per cent from a few weeks to months, and the serum cholesterol value had increased to approximately 300 mg per hundred cubic centimeters or higher. However, in six of the patients (cases 1, 13, 21, 27, 29 and 41) distressing symptoms of myxedema were manifest when the measurements of the basal metabolic rate gave values between minus 12 and minus 26 per cent. In these six instances the serum cholesterol was increased, the values ranging between 283 and 482 mg per hundred cubic centimeters, five patients showing concentrations above 300 mg per hundred cubic centimeters.

Three patients (cases 7, 16 and 36) operated on from ten to fifteen months ago have not as yet required thyroid medication for the alleviation of untoward symptoms of myxedema. The basal metabolic

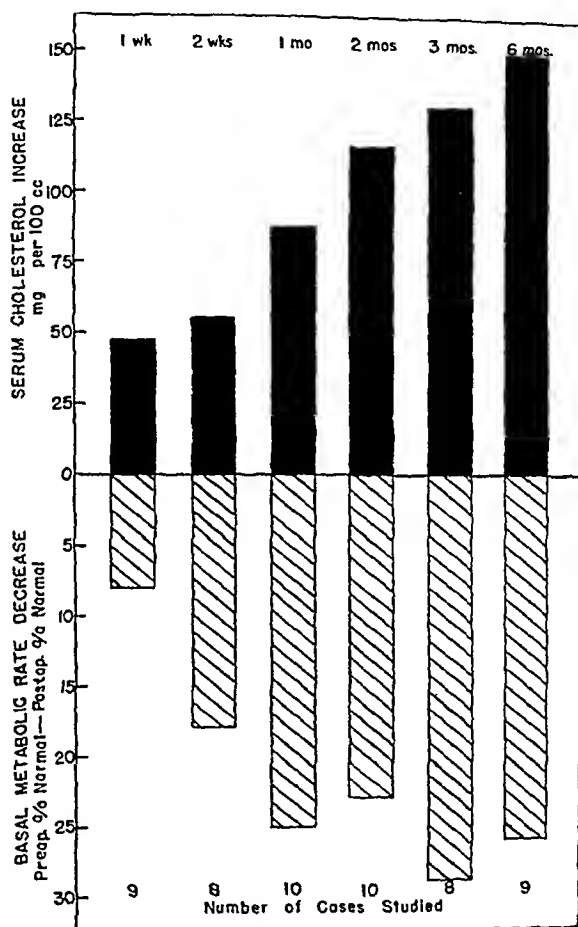
Serum Cholesterol Concentrations and Basal Metabolic Rates Before and at Varying Intervals After Total Ablation of the Normal Thyroid Gland

Case	Age	Sex	Diagnosis*	Before Operation			After Total Thyroidectomy												Thyroid Medication, Daily Dosage
				B M R Deviation, per Cent	Serum Cholesterol, Mlg per 100 Cc	B M R Deviation, per Cent	1 Week	2 Weeks	1 Month	2 Months	3 Months	4 Months	5 to 6 Months	9 to 10 Months	12 Months				
1 W D	22	M	O H F	- 8	92	-16	-32	140	-32	152	-27	-26	283†	-26	204	-28	260	1/4 to 1/2 gr	
2 L M	23	M	O H F	- 2	96	-18	-34	208	-30	203	-25	171	-27	†	202	-34	181	1 to 1/2 gr	
3 A R	50	M	N O	- 2	101	-20	-37	†	-30	203	-41	128†	-30	278	-34	202	1/4 gr		
4 R D	22	M	O H F	- 3	109	-22	-31	191	-29	203	-30	†	-30	278	-34	202	1/4 to 1/2 gr		
5 W B	63	M	O H F	-10	117	-21	-16	234	-20	203	-27	149	-30	278	-34	202	1/4 to 1/2 gr		
6 M W	54	M	A P	- 7	119	-12	-19	135	-22	310†	-27	149	-30	278	-34	202	1/4 to 1/2 gr		
7 E W	27	M	O H F	+ 5	127	+ 5	-19	135	-22	310†	-27	149	-30	278	-34	202	1/4 to 1/2 gr		
8 L B	44	F	O H F	- 9	132	-22	-32		-25	310†	-27	149	-30	278	-34	202	1/4 to 1/2 gr		
9 F Z	21	M	O H F	+ 1	138	- 8	-32		-25	310†	-27	149	-30	278	-34	202	1/4 to 1/2 gr		
10 H G	22	M	O H F	+ 7	138	-21	-33	280	-28	317	-27	†	-30	278	-34	202	1/4 to 1/2 gr		
11 B C	35	F	O H F	- 1	145	-24	-33	280	-15	317	-27	†	-30	278	-34	202	1/4 to 1/2 gr		
12 F O	35	M	O H F	- 4	154	-24	-33	280	-15	317	-27	†	-30	278	-34	202	1/4 to 1/2 gr		
13 S B	51	F	O H F	+ 4	154	-11	-33	280	-15	317	-27	†	-30	278	-34	202	1/4 to 1/2 gr		
14 O O	66	M	O H F	+ 9	154	-23	-36	207†	-15	317	-27	†	-30	278	-34	202	1/4 to 1/2 gr		
15 S B	47	F	O H F	+13	161	-23	-36	207†	-15	317	-27	†	-30	278	-34	202	1/4 to 1/2 gr		
16 B Z	45	F	O H F	+ 5	167	-16	-30	214	-27	364	-27	250	-30	305	-30	408	1/4 to 1/2 gr		
17 W M	63	M	N O	- 5	168	-11	-21	214	-33	320†	-31	305	-30	†	408	397	1/4 gr		
18 F D	18	M	O H F	-12	172	-28	-21	214	-26	320†	-36	323†	-30	305	294	294	1/4 gr		
19 F T	52	M	N O	0	180	+ 1	-15	180†	-25	180†	-32	435	-35	381	281	281	1/4 to 1/2 gr		
20 M O	57	M	A P	-21	192	-26	-34	347†	-34	347†	-32	435	-35	381	281	281	1/4 to 1/2 gr		

21 L M	55	M	CH F	+ 6	200	-12	232	-34	-21	345	-26	400†	-28	\$	-32	1/4 gr
22 A B	59	M	A P	- 4	211			-28	-30	298†	-31	315	-20	205		1/2 to 1/2 gr
23 M V	59	F	A P, D	-13	231	-17		-22	-33		-26	343†	-18			1/8 gr
24 M P	53	M	A P	-15	240	-14	311†	-30	-37	†	-34		-27			1/4 gr
25 G M	45	F	CH F, D G T	- 6	250	-11	192	-24	304							1/4 to 1/8 gr
26 M F	48	M	A P	-14	251			-16	-33	150†	-30	†	-30			1/2 to 1/8 gr
27 R S	57	F	A P, D	+ 3	292		+ 3	-19	309†	-26	-19		-23		†	1/10 gr
28 W B	55	M	CH F, P D	+ 9	294	- 2		-16	388†	-22	-24	410	-27		500	1/4 gr, 1 mo
29 E P	58	F	A P	-23	298			-23	-21	482†	-20	435§	-25			1 to 1/4 gr
30 R M	14	M	N C		180				248	394†	-42	†	-25			1/8 gr
31 H G	43	F	CH F	- 7		-19		-38	373†	292	-36	345	-28			1/2 to 1/8 gr
32 T O	64	M	A P	-19		-27	182	-20	-34	319	-33		-31			1/4 gr
33 M S	46	M	A P	- 8		-21	282	-37	231†	†	-25		-31			1/4 gr
34 H K	60	M	A P	-17		-29	189	-22	278	-30			-31			1/4 to 1/8 gr
35 S M	48	M	A P	+ 7		-34	357	-27	†				-26			1/4 gr
36 G F	52	M	CH F	- 2		-14		-23	-31	269	-28	286	-22			1/4 to 1/8 gr
37 M A	19	F	N C	- 7		-17		-36	-41	400†	-18		-29			1 to 1/8 gr
38 S F	52	M	A P			-28	162	-37	234	-31		520†				
39 B K	50	F	CH F	+14		-11		+12	237	+ 7	368					
40 H B	27	F	CH F	- 9				-21	263	-23	-30					1/8 gr
41 B R	48	F	CH F	+ 3		-16	294	-10	325	-14	404†	250	-35			1/8 gr
42 G O	65	M	A P	-13		-17	197	-23	322	-34	301	280†				1/8 gr
43 J R	63	M	CH F	+24		+ 3		-22	328	-28	424†					1/4 gr
44 M G	39	F	CH F	+ 3		-18		-3	400†	-12	295		-23			1/8 gr
45 E M	46	F	CH F	- 4		-24		-23	360†	-34	†					1/4 to 1/8 gr
46 J T	59	M	CH F	- 3		-10		-31	471	-28	†	330				1/2 to 1/8 gr
47 M H	51	M	A P	+ 5		+ 3	148	-4	181	342	-28			323		

* In the list of conditions diagnosed, CH F indicates congestive heart failure, N C, noncardiac condition, A P, angina pectoris, D, diabetes, P D, Paget's disease, and D G T, dextrose tolerance curve of diabetic type
† Thyroid medication instituted at the time of the appearance of untoward symptoms of myxedema
‡ Appearance of symptoms of advanced myxedema, thyroid induction withheld for observation
§ Thyroid medication discontinued for study or against advice

rates in these patients have been persistently low (table) In two of them the highest serum cholesterol values obtained at any time since operation were 181 and 303 mg per hundred cubic centimeters (cases 7 and 36) and in the third (case 16) 450 mg The latter patient was the only one who maintained a cholesterol level significantly above 300 mg per hundred cubic centimeters for many months, in the absence of a concomitant disease associated with a high serum cholesterol level, and



Relationship between the average changes in the serum cholesterol concentration and average changes in the basal metabolic rate following total thyroidectomy. The values presented were obtained in patients on whom both measurements were made preoperatively, and who after operation had not yet received thyroid medication. In two of the six patients whose cholesterol concentrations were measured one week after operation, the basal metabolic rates for the period were obtained by interpolation from the values obtained preoperatively and two weeks postoperatively. The average preoperative basal metabolic rate for all cases represented was minus 4 per cent, and the average serum cholesterol value was 174 mg per hundred cubic centimeters.

yet did not require thyroid medication for the control of untoward symptoms of myxedema.

Since the untoward symptoms of myxedema usually developed when the level of the metabolic rate was maintained significantly below minus 30 per cent, the extent of decrease in the basal metabolic rate which could be induced in a given patient by total thyroidectomy was proportional to the height of the preoperative basal metabolic rate (table). To cite two extreme instances from our series, the patient in case 20, whose preoperative basal metabolic rate was minus 24 per cent, required thyroid medication after a further decrease in the basal metabolic rate of only 10 per cent (minus 34), and the patient in case 14, whose preoperative basal metabolic rate was plus 9 per cent, required thyroid medication after a net decrease in the basal metabolic rate of 45 per cent (minus 36).

Effect of Small Doses of Thyroid Medication on the Serum Cholesterol, the Basal Metabolic Rate and the Clinical Signs and Symptoms of Myxedema—Since thyroidectomy was performed in patients with chronic heart disease for the therapeutic purpose of inducing hypothyroidism, according to the considerations outlined elsewhere,¹⁰ the mild signs and symptoms of myxedema were allowed to persist in order to maintain the basal metabolic rate at a low level. Small amounts of thyroid substance were administered when the untoward symptoms of myxedema developed. The amount of thyroid substance required to control the symptoms and at the same time to maintain the basal metabolic rate at a low level varied between $\frac{1}{8}$ and $\frac{1}{4}$ gram (81 and 324 mg) a day, the dosage being adjusted in each patient by trial. When the optimum amount of thyroid was administered, significant decreases in the serum cholesterol concentrations resulted (table). Thyroid medication was usually indicated between the end of the first and the sixth postoperative months, the period during which the serum cholesterol concentrations showed progressive increases, although the basal metabolic rates showed minor or no decreases (figure).

10 Blumgart, H. L., Levine, S. A., and Berlin, D. D. Congestive Heart Failure and Angina Pectoris. The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch Int Med* **51** 866 (June) 1933. Berlin, D. D. Therapeutic Effect of Complete Thyroidectomy on Congestive Heart Failure and Angina Pectoris in Patients with no Clinical or Pathological Evidence of Thyroid Toxicity. II. Operative Technique, *Am J Surg* **21** 173, 1933. Blumgart, H. L., Riseman, J. E. F., Davis, D., and Berlin, D. D. Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, *Arch Int Med* **52** 165 (Aug) 1933.

COMMENT

Blumgart and his associates have demonstrated¹¹ that patients with chronic heart disease and no hyperthyroidism are benefited by the decreased burden on the heart which obtains in hypothyroidism induced by total ablation of the thyroid gland. The changes in the basal metabolic rate and the serum cholesterol which occur after operation together with the relationship of these changes to the clinical aspects of hypothyroidism are reported here.

In the group of twenty-nine patients in whom the basal metabolic rates and cholesterol concentrations were measured before operation (table) twenty-five had basal metabolic rates between plus 9 and minus 13 per cent. There was no evident correlation between the serum cholesterol concentration and the basal metabolic rate before operation. However, in the other four (cases 20, 24, 26 and 29), all of whom suffered from angina pectoris, the basal metabolic rates ranged between minus 14 and minus 24 per cent, and in three of these the serum cholesterol values were between 240 and 298 mg per hundred cubic centimeters. It is believed, in retrospect, that signs suggestive of myxedema were present before operation in one of them (case 29). In the other three patients there were no clinical evidences of decreased thyroid activity before operation. Pathologic studies of the thyroid glands from the four patients were made by Dr. Monroe Schlesinger, and revealed normal observations.

In a recent investigation,⁹ studies of the basal metabolic rate and serum cholesterol values in a group of normal subjects showed that persons with no clinical evidence of hypothyroidism may have basal metabolic rates as low as from minus 20 to minus 35 per cent, and that the serum cholesterol concentration in such persons may be increased to between 230 and 290 mg per hundred cubic centimeters.

The basal metabolic rate decreased following total thyroidectomy, and remained persistently low in forty-seven of the forty-eight patients studied in this series. Basal metabolic rates as low as from minus 41 to minus 47 per cent were observed postoperatively in four. Such levels could not be maintained, because thyroid medication was required to control untoward symptoms of myxedema. Although it was impossible to measure the lowest levels of metabolic rate which patients deprived of all thyroid tissue might have attained if allowed to continue without thyroid medication, it is believed that the levels from minus 41 to minus 47 per cent, which were attained after the end of the first postoperative month, represent the approximate metabolic levels of completely thyroidoprival persons. This observation is in accord

11 Friedman, H. F., and Blumgart, H. L. Treatment of Chronic Heart Disease by Lowering the Metabolic Rate. The Necessity for Total Ablation of the Thyroid, *J. A. M. A.* **102** 17 (Jan. 6) 1934. Footnote 10.

with the concept of Means¹² and others that the normal thyroid activity controls from 40 to 45 per cent of the caloric requirements of the human subject, and with the fact that basal metabolic rates lower than minus 47 per cent of normal² are rarely if ever encountered in hypothyroidism, either of idiopathic or postoperative origin

Decreases in the basal metabolic rate following total thyroidectomy were accompanied by increases in the serum cholesterol concentration, the highest cholesterol value obtained being 543 mg per hundred cubic centimeters, in a patient who showed marked symptoms of myxedema at the time of the test. The serum cholesterol values obtained in the patients with postoperative hypothyroidism were similar to those obtained by other investigators in patients with spontaneous myxedema. Thus, Mason, Hunt and Hurxthal² reported cholesterol values as high as 500 mg per hundred cubic centimeters associated with markedly lowered basal metabolic rates in patients with spontaneous myxedema, and Bronstein^{3a} reported a blood cholesterol value of 782 mg per hundred cubic centimeters in a child with hypothyroidism. The highest serum cholesterol values are obtained in those patients who show the most advanced clinical symptoms¹³ (table). When the more serious symptoms of myxedema were controlled by appropriate thyroid medication, the serum cholesterol value was generally maintained at a level of about 300 mg per hundred cubic centimeters.

The patient in case 39 (table) is the only one in a consecutive series of seventy operated on at this hospital who did not show a low basal metabolic rate following total thyroidectomy. Measurements of the basal metabolic rate in this case gave values of plus 14 per cent pre-operatively and plus 12 and plus 7 per cent at the end of the first and second postoperative months, respectively. A measurement at the end of the fourth postoperative month was unsatisfactory. The serum cholesterol value one month after operation was 237 mg per hundred cubic centimeters and showed further marked increases to 368 and 520 mg at the end of the second and fourth postoperative months, respectively. The progressive increase in serum cholesterol values together with clinical manifestations of myxedema in this patient offered evidence that a state of hypothyroidism had been induced by the operation and that the persistence of a basal metabolic rate at a normal level may have been due to inability to obtain a basal test.

In six patients of this series the untoward symptoms of myxedema, such as weakness of the legs, drowsiness, irritability and puffiness of the face, hands and feet, were manifest when the basal metabolic rate was reduced only from minus 12 to minus 26 per cent. In four of the six, the serum cholesterol concentrations were increased above

12 Means, J. H. Personal communication to the authors.

13 Mason, Hunt and Hurxthal² Bronstein^{3a}

300 mg per hundred cubic centimeters Although basal metabolic rates similarly reduced are encountered in normal persons, serum cholesterol values of this magnitude are not obtained¹⁴ These considerations suggest that true measurements of the basal metabolism may not have been obtained in some of the six with untoward symptoms of myxedema This suggestion is strengthened by the fact that some of the patients had shown lower basal metabolic rates earlier in the postoperative course, before the development of the advanced symptoms of myxedema

On several occasions we have been unable to obtain duplicate measurements of the basal metabolic rate which agreed within 5 per cent In these instances the serum cholesterol measurements have been a useful adjunct to clinical observations

That the serum cholesterol concentration may give evidence of hypothyroidism when the basal metabolic rate does not is shown by observations on patients with myxedema after the administration of *di*-nitro-phenol and *di*-nitro-*ortho*-cresol When the basal metabolic rate is increased to or above normal by these drugs in patients with myxedema the clinical signs and symptoms and the high serum cholesterol concentration persist unchanged¹⁵

There seems to be a general belief that myxedema and hypercholesteremia predispose one to arteriosclerosis There is little evidence from observations in man, however, to support these theories¹⁶ Roentgenologic studies of the blood vessels in six patients in this group who had hypothyroidism and associated hypercholesteremia of a year's duration showed no apparent increased density

Since the level of the basal metabolic rate at which the untoward symptoms of myxedema develop is usually about minus 30 per cent, only a moderate reduction in the basal metabolic rate after total thyroidectomy can be effected in those patients who before operation have lowered basal metabolic rates¹⁷ (table)

Measurements of serum cholesterol concentration have served as an adjunct to clinical impressions in the evaluation and control of the

14 Mason, Hunt and Hursthal² Volk, Abrams and Gilligan⁹

15 Dodds, E C, and Robertson, J D Clinical Applications of Dinitro-Cresol, *Lancet* 2: 1137 and 1197, 1933 Rabinowitch, I M, and Fowler, A F Dinitrophenol, *Canad M A J* 30: 128, 1934

16 Means, J H, and Richardson, E P The Diagnosis and Treatment of Diseases of the Thyroid, in Christian, H A Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 1929, vol 4 Peters, J P, and Van Slyke, D D Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol 1, p 238

17 Blumgart, H L, Davis, D, Riseman, J E F, Berlin, D D, and Weinstein A A Treatment of Angina Pectoris and Congestive Failure by Total Ablation of the Thyroid XI Résumé of Results in Treating Seventy-Five Patients During the Last Eighteen Months *J A M A*, to be published

hypothyroid state which develops following total thyroidectomy. Since the value of the measurement does not depend on the cooperation of the patient, it has proved at times to be a useful laboratory test in determining the presence or degree of hypothyroidism in patients who are unable to obtain the relaxation necessary for measurement of the true basal metabolic rate. The measurement of serum cholesterol is also of considerable value as an adjunct to clinical impressions in the estimation of the degree and course of hypothyroidism when, during the development of the hypothyroid state, the basal metabolic rate has reached and is maintained at a low level.

SUMMARY

1 Simultaneous measurements of the serum cholesterol concentration and basal metabolic rate have been made in a group of patients before and at intervals during the development of the hypothyroid state after total ablation of the normal thyroid gland.

2 Following total thyroidectomy, the serum cholesterol value increases as the basal metabolic rate decreases and as the clinical evidences of hypothyroidism become manifest. The highest serum cholesterol concentration obtained in any patient was 543 mg per hundred cubic centimeters and the lowest basal metabolic rate was minus 47 per cent.

3 Appreciable changes in the basal metabolic rate and serum cholesterol concentration were generally evident by the end of the first postoperative week. Striking changes in the values were observed by the end of the first postoperative month. During the following few months the basal metabolic rate showed only minor, if any, decreases, whereas the serum cholesterol concentration gradually increased and the clinical course of hypothyroidism gradually progressed.

4 When the untoward symptoms of myxedema became manifest, the serum cholesterol concentration was usually increased to 300 mg per hundred cubic centimeters or above, and the basal metabolic rate was usually decreased to minus 30 per cent or below.

5 Small doses of thyroid medication, administered to control the untoward symptoms of myxedema, caused slight increases in the basal metabolic rate and significant decreases in the serum cholesterol concentration.

6 In a few instances a high serum cholesterol value confirmed the clinical finding of untoward symptoms of myxedema when the basal metabolic rate was not markedly low. In other instances, when duplicate measurements of the basal metabolic rate which agreed within 5 per cent could not be obtained, the serum cholesterol concentration was a valuable adjunct to clinical impressions in estimating the degree and course of the hypothyroid state.

A RAPID QUANTITATIVE METHOD FOR EXAMINING THE URINE IN RENAL DISORDERS

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SAN FRANCISCO

The diagnosis and treatment of Bright's disease depends, in part, on the understanding the physician has of the renal lesion with which he is dealing. As clinical practitioner,¹ he would prefer to formulate a picture of the disease without bothering with numerical values and calculations. A knowledge of the rate at which formed elements are passed in the urine, together with the quantitative estimation of the rate of elimination of protein, greatly increases the value of the urinalysis. The Addis method² of collection of urine and enumeration of the formed elements of the urine and estimation of urine protein provides the necessary information, but is of little value to the clinical practitioner, because it is time-consuming and does not provide constantly uniform conditions which enable him to tell at a glance the nature of the renal lesion. Constantly uniform conditions can be obtained in the modified method described here by a manipulation of the urine so as to eliminate variable times and rates of excretion. This method reduces the sediments of all patients to a uniformity which permits direct comparison and provides a series of pictures representing at a glance the nature and intensity of the renal lesion. The method allows rapid calculation of the rate at which cells and casts are excreted in the urine and at the same time assures a concentrated specimen of urine. The urine must be concentrated and the reaction must be acid, otherwise some of the formed elements will dissolve.

METHOD

Enumeration of Formed Elements—The patient is instructed to go without fluids after breakfast the day before the test. In the evening of the day, on retiring, he empties the bladder, discards the urine and notes the time of doing so. The next morning he passes urine into a collecting bottle, again notes the time and brings the specimen to the laboratory for examination.

The volume of the collected urine is measured in a 1,000 cc graduate cylinder. The urine is well mixed. A volume equal to the number of hundred cubic centimeters in the total urine (i e, 1 per cent of the total) is placed in a 15 cc

From the Department of Medicine, Stanford University School of Medicine

1 Addis, T. Science and Practice in Bright's Disease, *Ann Int Med* 6
1077 (Feb) 1933

2 Addis, T. A Clinical Classification of Bright's Disease, *J A M A* 85
163 (July 18) 1925

graduate centrifuge tube. The urine is then centrifugated until all the elements are deposited at the bottom of the tube. The greater part of the supernatant urine is now pipetted off with a capillary pipet until it is reduced to the proper volume for calculation. If the centrifugated portion is from an eleven or twelve hour specimen, the volume must be 0.5 cc, if from a nine to eleven hour specimen, the volume must be 0.4 cc, and if from a seven to nine hour specimen, 0.33 cc. The sediment is then mixed with the aid of a pipet, and a drop is transferred to a ruled blood counting chamber. The average number of elements in 0.1 c mm (one small square) is then counted. This number is divided by 2. The resulting figure is the number of million elements excreted by the patient in twelve hours. In making the count the low power objective should be used for counting casts, and the high power for the cells. This method is applicable to all specimens of urine, and gives the same picture for all similar renal lesions.

The number of elements in a twelve hour specimen is calculated by the Addis method as follows

$$\frac{\text{Number of elements in 1 small square} \times \text{volume of specimen}}{0.0001 \text{ cc}} \times \frac{12 \text{ hour volume}}{\text{Volume centrifugated}} \\ = \text{number of elements excreted in twelve hours}$$

In these fractions it is possible to have all except two items constant. The two variable items are (1) the number of elements counted in one small square, and (2) the twelve hour volume. It is possible to make the quotient of the fraction, $\frac{\text{Twelve hour volume}}{\text{volume centrifugated}}$, constant by having the denominator (volume centrifugated) always equal to 1 per cent of the numerator (twelve hour volume). When this is done the only variable item influencing the result is the number of elements counted in one small square. Furthermore, when, instead of a twelve hour specimen the patient brings an eight, nine, ten or eleven hour specimen, it is necessary to correct the volume to twelve hours. But the calculation for this can be avoided by taking the centrifugated sediment up in, say, eight-twelfths of 0.5 cc, or 0.33 cc, for an eight hour specimen, nine-twelfths, or 0.37 cc, for a nine hour specimen, ten-twelfths, or 0.41 cc, for a ten hour specimen, or eleven-twelfths, or 0.45 cc, for an eleven hour specimen. Because the error in the final result is small, it is unnecessary to correct closer than a two hour difference. Thus, a seven to nine hour volume is taken up in 0.33 cc, and a nine to eleven hour volume is taken up in 0.4 cc, and the different items can be so arranged that the number of elements counted when divided by 2 will give the result in millions of elements per twelve hour specimen.

For example 1. Given a twelve hour specimen of urine, the volume is 400 cc and 12 red blood cells are counted in one of the nine squares of the counting chamber. Therefore, according to the formula $\frac{12 \times 0.5 \text{ cc} \times 400 \text{ cc}}{0.0001 \text{ cc} \times 4 \text{ cc}} = 6,000,000$ red blood cells

2. Given a ten hour specimen, the volume is 333 cc, with the precipitate taken up in 0.4 cc (note that the volume does not change in the calculation) and 12 red blood cells are counted in one of the nine squares

$$\text{Therefore } \frac{12 \times 0.5 \times 333 \text{ cc}}{0.0001 \times 3.3} = 6,000,000 \text{ red blood cells}$$

Estimation of Urine Protein—In order to know the rate of output of albumin, it is necessary to know the quantity excreted over a definite period of time. Addis² calculated the excretion of protein of normal and diseased kidneys for twelve hour periods. By simple mathematics, the volume of urine excreted during twelve hours can be estimated from the volumes collected in from eight to eleven

hours Then, with 1 cc of urine, a calculation of the percentage of protein present is made, and from this information the excretion of protein in twelve hours is determined For this estimation the simple and rapid procedure for measuring albumin described by Lashmet and Newburgh³ has been adapted The turbidity, or cloud, produced by adding sulphosalicylic acid to the urine containing protein is compared with that of a standard turbidity solution representing a known protein content

Stock Solution To about 200 cc of distilled water in a 500 cc volumetric flask, 50 cc of a tenth-normal solution of sodium hydroxide, U S P, and 8 Gm of cupric sulphate, U S P (hydrous), are added The volume of 500 cc is made up with distilled water

Standard Solution After shaking the stock solution vigorously to insure uniform suspension, exactly 4 cc of this mixture is transferred to a 100 cc graduate cylinder and tap water is added up to the 50 cc mark The turbidity of this mixture is the same as that produced by a 0.1 per cent solution of protein, 0.1 Gm per hundred cubic centimeters, when sulphosalicylic acid is used This solution can be kept in a flask for use when wanted The turbidity does not change on standing It must, however, be shaken several times before using

In order to determine the amount of protein in the urine, 1 cc of the centrifugated urine is placed in a 100 cc graduate cylinder, and a 2 per cent solution of sulphosalicylic acid is added to bring the volume up to 25 cc The standard solution is placed in a second 100 cc cylinder for comparison If the turbidity of the mixture is the same as that of the standard solution the urine contains 0.1 per cent protein If the turbidity is greater than that of the standard solution, the mixture should be diluted with tap water until it compares with the standard Correction for the dilution is done by multiplying 0.1 per cent by the number of times the 25 cc volume has been diluted, then the corrected figure is multiplied by the number of cubic centimeters of urine excreted in twelve hours The result is the number of grams of protein excreted in twelve hours If the turbidity of the mixture is less than that of the standard solution, urine should be added until the same turbidity as that of the standard solution is obtained The twelve hour volume is then divided by the number of cubic centimeters of urine added and multiplied by 0.1 per cent Not more than 5 cc of urine should be added to the reagent, if no cloud is formed with this amount, the albumin content of the urine is negligible This is a rough estimate of the rate of excretion of protein, and is applicable for practical use in determining the type or the progress of a renal lesion

COMMENT

The table gives the average number of elements in the urine and the average output of albumin per twelve hours in normal and pathologic states There is a wide range, particularly in the output of protein from which these averages are determined, so that individual variations may be considerable Furthermore, there are gradations between the various stages of renal lesions

In glomerular nephritis in the initial stage about 2 casts per field are seen under low power magnification, and a large number of red

³ Lashmet, F H, and Newburgh, L H An Improved Concentration Test of Renal Function II A Simple Method for Measuring Proteinuria, *J A M A* 100 1328 (April 29) 1933

blood cells and white blood cells per field are seen under high power magnification, in the degenerative (active) stage 4 or more casts per field are seen under low power, and a moderate number of red blood cells and white blood cells under high power, magnification, in the latent stage a few casts, about 2 in the nine squares, are seen under low power, and a few red blood cells and white blood cells per field under high power, magnification, in the terminal stage about 1 broad cast per field is seen under low power, and a moderate number of red blood cells and white blood cells under high power, magnification. In degenerative Bright's disease about 1 cast per field is seen under low power, and no, or very occasional, red blood cells and a moderate number of white and epithelial cells under high power, magnification. In arteriosclerotic Bright's disease few casts, 1 or 2 per nine squares, are seen under low power, and an occasional red and white blood cell under high power, magnification.

Average Cast and Cell Counts

	No of Cases	Casts	Red Blood Cells	White Blood Cells	Protein, Mg
Glomerular nephritis					
Initial	50	690,000	405,000,000	48,000,000	550
Latent	100	48,000	16,000,000	2,400,000	369
Degenerative or active	65	1,850,000	34,000,000	14,000,000	5,730
Terminal	50	398,000	26,400,000	10,000,000	3,550
Degenerative Bright's disease†	10	438,270	127,600	13,966,000	4,305
Arteriosclerotic Bright's disease	12	40,000	200,000	1,000,000	200
Normal	75	5,000	1,000,000	1,000,000	Negligible (30)

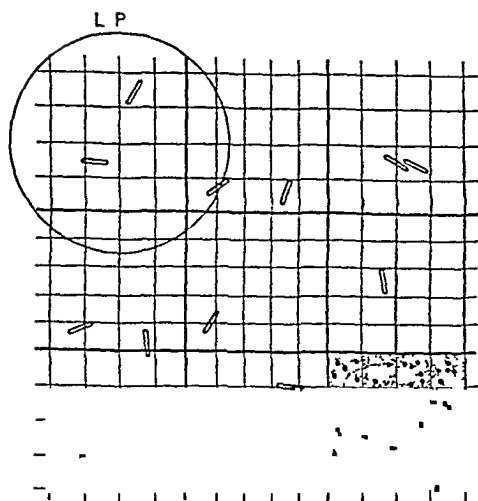
* From unpublished observations of T. Addis

† These average figures are from cases of true lipoid nephrosis and do not include other forms of degenerative Bright's disease

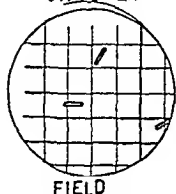
A comparison of the results of the two methods of enumerating the elements in the urine proves the new method to be satisfactory. While the difference in the two counts may be considerable, it is never so great that it creates a false impression. In the count of casts, for example, a difference between 40,000 and 100,000 or 1,000,000 and 5,000,000 can occur. This is of no consequence, however, when the diagnosis depends on whether or not there are 40,000 or from 1,000,000 to 4,000,000 casts. When no casts are seen, or when 1 cast is seen in nine small squares, one might expect the output to be a normal number of casts, or as many as 55,000. At first thought this seems a source of gross misinterpretation, but unless the other elements are present in abnormal numbers, one can hardly regard the specimen of urine as anything but normal. Even in mild arteriosclerotic Bright's disease there would be a slight increase in the number of cells and in the output of protein to aid in the diagnosis of the lesion.

The percentage of error in counting red blood cells and white blood cells, in comparison with the Addis method, may sometimes be as high

INITIAL STAGE

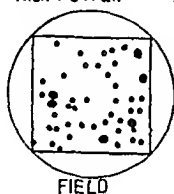


LOW POWER



FIELD

HIGH POWER

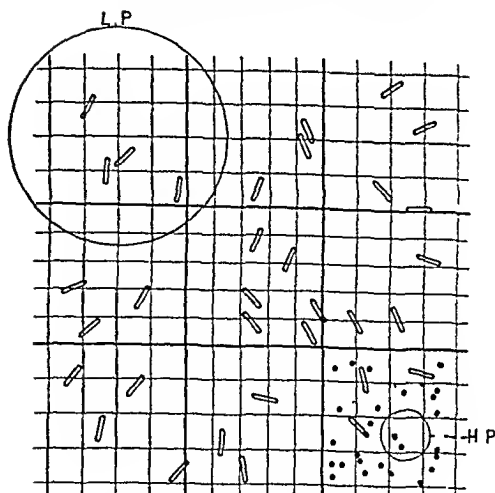


FIELD

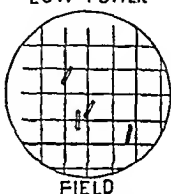
ALBUMIN

550 MG

DEGENERATIVE STAGE

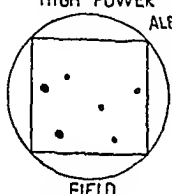


LOW POWER



FIELD

HIGH POWER

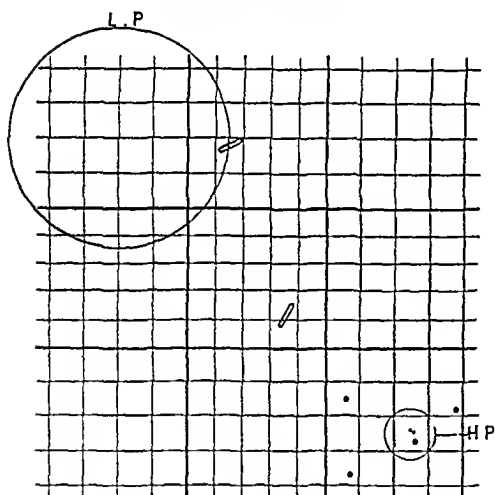


FIELD

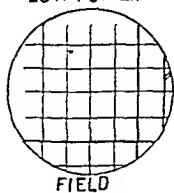
ALBUMIN

6790 MG

LATENT STAGE

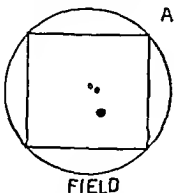


LOW POWER



FIELD

HIGH POWER

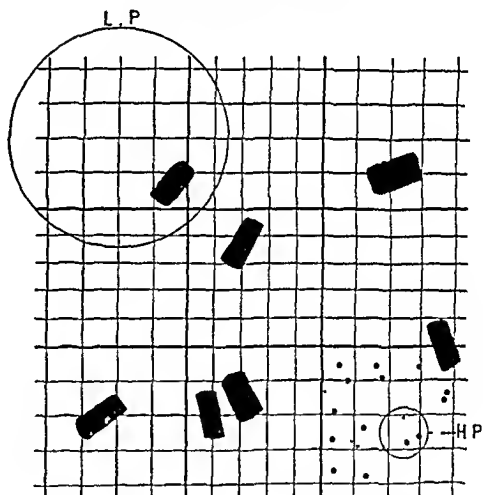


FIELD

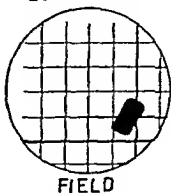
ALBUMIN

369 MG

TERMINAL STAGE

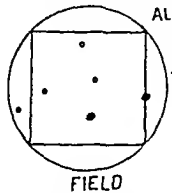


LOW POWER



FIELD

HIGH POWER



FIELD

ALBUMIN

3550 MG

Chart 1—Diagrams of the microscopic appearance of the urinary sediment in glomerular nephritis. Each large ruled square represents the blood counting chamber. The open oblong figures represent casts seen with the low power objective and the solid oblong figures, casts appearing with renal failure. Red and white blood cells are illustrated in the small square in the lower right of each diagram, the white cells indicated by the solid circle and the red cells by the open circle. The areas seen by low and high power objectives are indicated by circles. Both high and low power fields are illustrated below each square. The cells are not shown in the low power fields. The average twelve hour output of albumin is indicated for each condition.

as 500 with numbers below 1,000,000 This makes no difference in the picture of the renal lesion when any number up to 1,000,000 in twelve hours is considered normal, for example, by the Addis method the red blood cell count may be 100,000 and by the modified method, 500,000 For numbers above 1,000,000, errors of 300 per cent can occur in the count but do not alter the picture, for example, by the Addis method the red blood cell count may be 10,000,000 and by the modified method, 30,000,000

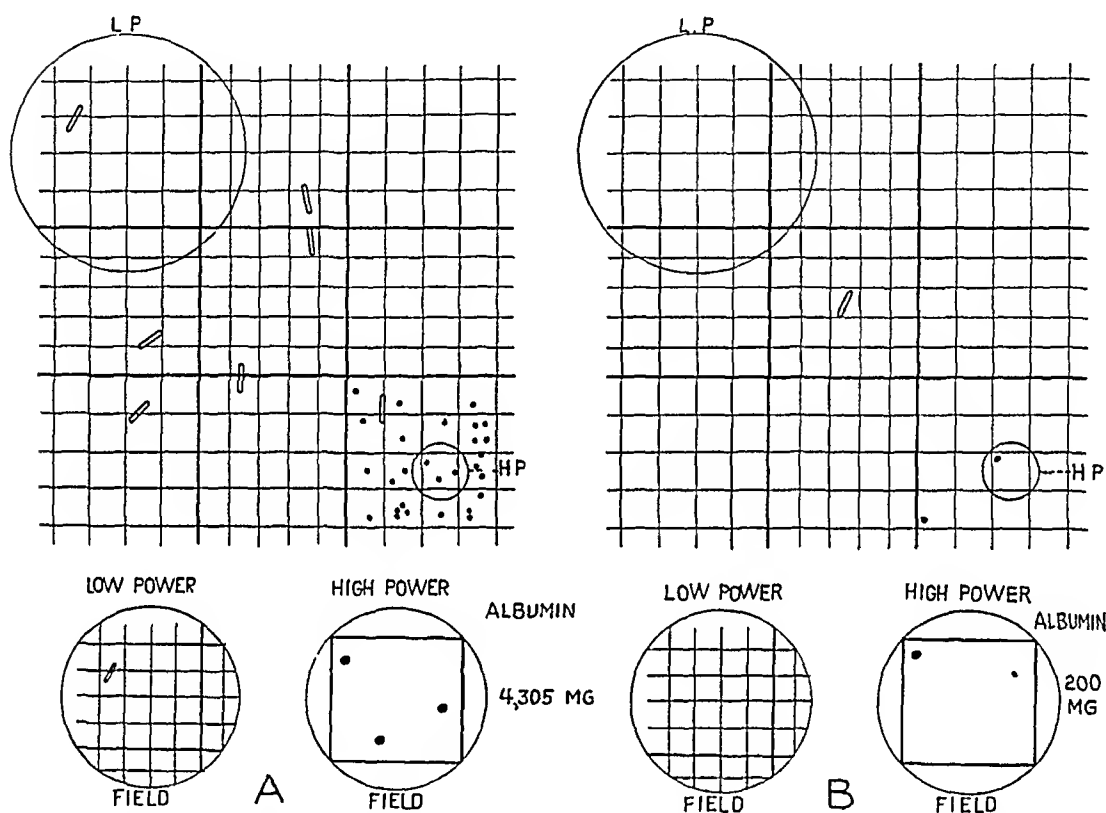


Chart 2—Diagrams of the microscopic appearance of the urinary sediment in (A) degenerative Bright's disease and (B) arteriosclerotic Bright's disease. Interpretation of the diagram is given in the legend for chart 1. The average twelve hour output of albumin is indicated for each condition.

The error in the determination of albumin is never great enough to change the impression of the degree of damage to the kidney, provided the urine is concentrated and the volume fairly accurately measured.

In conclusion, it can be said that the clinical practitioner can obtain a constantly uniform picture, in conjunction with other clinical evidence, of every pathologic state of the kidneys by quick and easy means and with average office facilities. A little practice with the technic of counting the sediment is all that is required. After a few practice determinations a quick estimation of the type and activity of the renal lesion should be possible.

NITROGEN AND SULPHUR METABOLISM IN BRIGHT'S DISEASE

V METABOLIC STUDY OF A PATIENT WITH EDEMA OF UNKNOWN ORIGIN

G PHILIP GRABFIELD, M D

MARGARET DRISCOLL, A B

AND

MILDRED G GRAY, A M

BOSTON

Patients suffering from chronic nephritis with renal edema tend to retain both nitrogen and sulphur when fed diets high in protein,¹ and even retain crystalline urea. On the other hand, it has been shown that patients with Bright's disease without renal edema tend toward a negative sulphur and nitrogen balance as the disease progresses.² The mechanism of these reactions is not clear, as it has been impossible to demonstrate an elevation of the nonprotein nitrogen level of the blood in patients retaining large quantities, whereas in patients without renal edema the nonprotein nitrogen level of the blood rises despite the negative balance. In the study of patients with renal edema it can be shown by a simple calculation that if the retained nitrogen and sulphur or urea is equally distributed throughout the body, easily measurable quantities should be demonstrable in the blood. It has always been assumed that the nitrogen and sulphur so retained are used to make up the depletion of the serum proteins, but for long periods nitrogen may be retained without an apparent variation in the serum protein values. On the other hand, it might be that such retained nitrogen and sulphur go into the edema fluid and are not recoverable. Such analyses as are available do not indicate that this is the case.³ There remains another hypothesis and that is that such nitrogen and sulphur are retained within all or some of the cells of the body and are stored there. The various hypotheses have been summarized recently by Moschowitz.⁵

The present report deals with the study of a patient with a curious chronic edema, obviously not of cardiac or of renal origin. The study

From the medical clinic of the Peter Bent Brigham Hospital

1 Grabfield, G P. *J Clin Investigation* **9** 311, 1930

2 Grabfield, G P. Nitrogen and Sulphur Metabolism in Bright's Disease
IV Retention of Urea in the Nephrosis Syndrome, *Arch Int Med* **52** 632 (Oct)
1933

3 Grabfield, G P. *J Clin Investigation* **10** 309, 1931

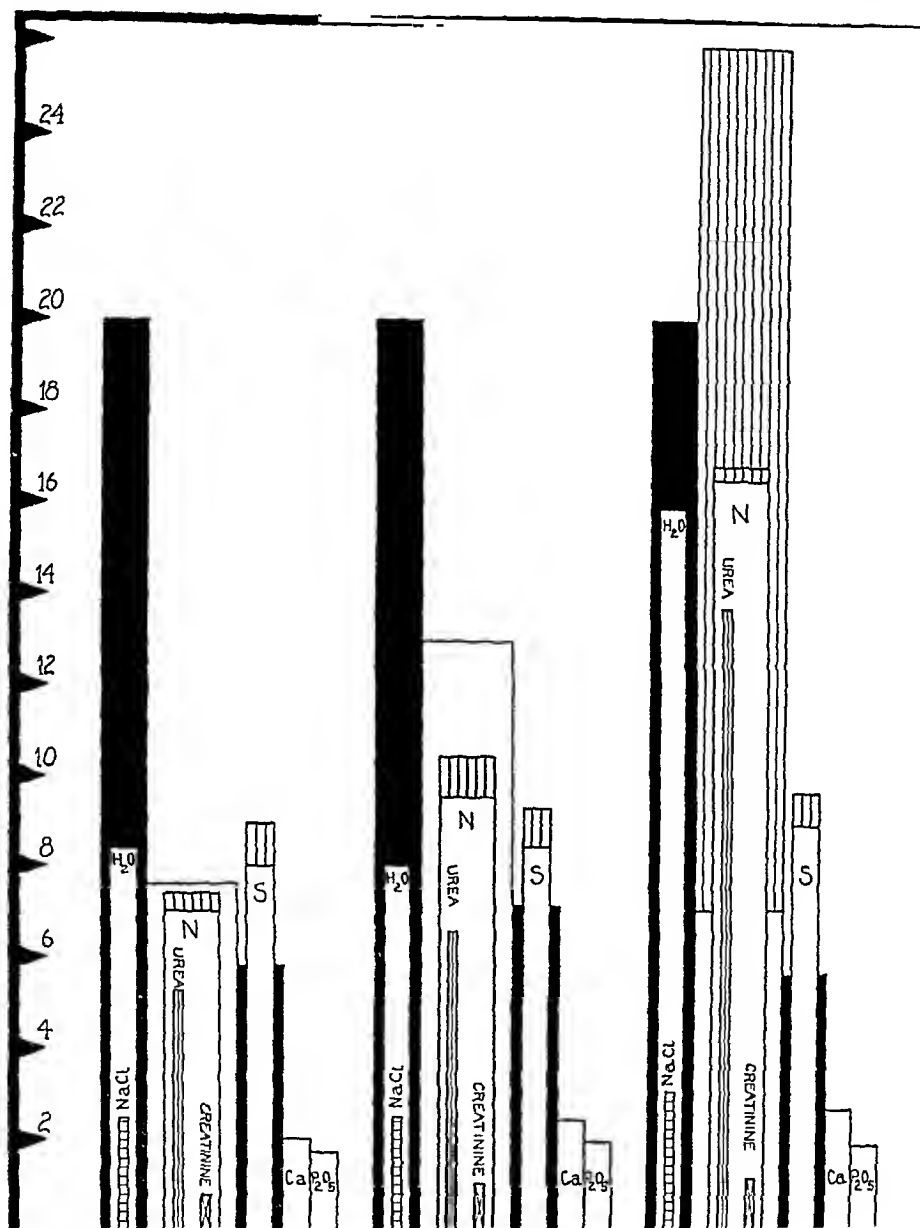
4 Peters, J P, and Van Slyke, D D. *Quantitative Clinical Chemistry*,
Baltimore, Williams & Wilkins Company, 1931, vol 1

5 Moschowitz E. Hypoproteinemia, *J A M A* **100** 1086 (April 8) 1933

Laboratory Observations for Metabolic Study During Three Periods

Date, 1933	Urine					Food					Blood and Fluid from Chest										Comment			
	Volume, Cc	Creatinine, Mg	Total Nitrogen, Gm	Total Sulphur, Mg	Urea + Ammonia Nitrogen, Gm	Chlorides, Gm	Calcium, Mg	Phosphate, Gm	Protein, Gm	Phosphorus, Gm	Sulphur, Mg	Calories	Total Protein, Gm per 100 Cc	Serum Albumin, Gm per 100 Cc	Serum Globulin, Gm per 100 Cc	Cholesterol, Mg per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc	Urea Nitrogen, Mg per 100 Cc	Creatinine, Mg per 100 Cc	Phosphate, Mg per 100 Cc		Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	
Period 1																								
1/23		810	8.1	530	5.8	1.6	190	1.11	49	0.86	6.4	1,891	8.3	2.7	5.6	95	29	10	1.3	3.1				
1/28	120	810	7.2	620	5.4	2.3	270	1.92	48	0.97	6.5	1,815	8.3	2.7	5.3		27							
1/31	855	660	7.3	550	5.6	3.1	160	1.66	45	0.88	7.6	1,797	7.5	2.8	4.7	115	18							Fibrinogen, 0.6 mg per 100 cc
1/7	665	640	6.5	690	5.1	2.6	180	1.72	45	0.81	5.69	1,817	7.5	2.8	4.7	115	18	1.1	1.1					
1/8	910	640	6.5	690	5.1	2.6	180	1.72	45	0.81	5.69	1,817	7.5	2.8	4.7	115	18	1.1	1.1					
1/9	610	600	5.9	730	4.7	1.2	150	1.60	46	0.93	5.85	1,814	11.1	1.9	2.2	30	17	8	1.1	1.1				Fluid from the chest
1/10	780	600	5.9	730	4.7	1.2	150	1.60	46	0.93	5.85	1,815	11.1	1.9	2.2	30	17	8	1.1	1.1				Daily average fecal nitrogen, 0.41 Gm, sulphur, 0.69 Gm
1/11		960	6.7	1,320	4.9	3.2	210	1.91	47	0.93	5.94	1,833												
1/12	930	1,080	7.2	1,110	5.9	3.0	290	2.07	46	0.87	5.78	1,820												
1/13	1,210																							
Period 2																								
1/14	930	1,010	9.0	1,260	6.9	3.1	320	2.10	77	1.29	7.01	1,807	6.9	3.0	3.9									Daily average fecal nitrogen, 0.96 Gm, sulphur, 0.69 Gm
1/15	935	1,040	15.1	1,150	6.5	1.9	270	1.91	90	1.24	890	1,965												Fluid from the chest
1/16									89	1.26	882	1,901												
1/17									82	1.22	820	1,681	6.9	3.0	3.9									
1/18	960	910	9.6	710	7.9	2.3	260	2.04	90	1.20	895	1,691												Daily average fecal nitrogen, 0.96 Gm, sulphur, 0.69 Gm
1/19	670	1,010	6.5	680	5.3	2.1	290	1.93	51	0.59	4.99	1,149												Fluid from the chest
1/20	670	990	7.9	420	5.0	2.3	230	1.86	87	1.05	6.69	1,671	8.0	2.6	5.4	160	25	11	1.1	1.1		10.1		
1/21	650	1,070	9.1	840	8.4	3.2	200	1.76	68	1.10	7.61	1,556	4.7	1.7	3.0	55	30	11	1.1	1.1				
1/21																								
Period 3																								
1/22									45	0.91	6.23	1,799												Urea, 10 Gm three times a day during this period
1/23									45	0.87	5.17	1,759												
1/24									38	0.75	4.83	1,591												
4/25	1,410	1,150	13.6	720	11.0	2.7	270	1.99	45	0.87	5.68	1,803												Daily average fecal nitrogen, 0.33 Gm, sulphur, 0.66 Gm
4/26	1,820	1,200	17.3	860	14.7	3.2	270	2.03	46	0.85	5.52	1,662												
4/27	2,025	1,110	19.9	960	17.4	3.2	310	1.89	45	0.85	5.52	1,662												
4/28	2,030	1,180	16.5	1,030	11.1	3.2	280	1.97	46	0.84	5.53	1,765												
4/29	1,100	1,060	15.9	850	12.6	3.0	210	1.76	45	0.90	5.87	1,721												
4/30	1,110	1,110	16.1	900	12.6	3.0	210	1.80	42	0.87	5.51	1,788												
5/2													7.8	2.6	3.2	125	32	12	1.1	1.1	3.6	10.4	19.1	Fluid from the chest
5/5													5.4	3.7	1.7	55	23	1.5	1.0	1.1	6.1	6.1	10.2	
5/12													7.9	2.7	3.2		24	8						

of this patient serves to test the hypothesis that the retention of nitrogen and sulphur is a function of the edema itself and bears no relation to the renal lesion. The history of this patient will be given in detail. It is sufficient to say here that the outstanding features shown were



Average daily excretion for three periods under the varying conditions of intake as shown in the table. The creatinine, urea, chlorides and total nitrogen are indicated in grams, the total sulphur, calcium and phosphorus pentoxide in hundred milligrams and the fluids in hundred cubic centimeters. The outer columns represent the intake, the inner columns the output.

generalized edema, including edema of the face, definite evidence of capillary damage in the periphery, and a comparatively high total protein level in the serum, with a reversal of the albumin-globulin ratio. The

detailed laboratory observations are given in the table. A case similar to the one reported here has recently been studied by Myers and Taylor,⁶ but their patient showed important retention of protein on a diet high in protein and, at times, a negative balance on a diet lower in protein.

We treated this patient as we have other patients observed in this series, giving her a carefully weighed, constant diet, adequate in calories and in protein, keeping the fluid level constant by making up the fluid of the ingested food to 2,000 cc per day with water. The detailed figures of the experiment are given in the table, and in the chart are presented the average daily figures of three periods of study, each including six or seven days. In the first period, a diet of 50 Gm of protein was given, in the second, an attempt was made to ingest 100 Gm of protein, and in the third, the preliminary diet was given plus 10 Gm of crystalline urea three times a day. During each dietary period blood and fluid from the chest were simultaneously withdrawn, and the various constituents determined. There was essentially no variation as a result of the dietary changes. The relation between the chemical constitutions of the two fluids approximates that between blood and spinal fluid. It will be seen that there was diuresis in the third period as a result of the administration of urea.

The contrast between this patient and the patient with a typical nephrosis syndrome in the metabolic reactions is apparent. There was no important retention of nitrogen in the first two periods, and there was a striking negative sulphur balance. The negative sulphur balance was increased during the period of diuresis, but during the same period there was apparently some retention of nitrogen. The low concentration of sodium chloride in the extra fluid excreted during the period of ingestion of urea may be an indication that the fluid comes from within the cells. From this contrast one may conclude that the retention of nitrogen and sulphur in patients with Bright's disease with renal edema is not a result of the edema itself.

REPORT OF A CASE

CASE 19—*History*—C M D, a married white woman, aged 32, was admitted to the hospital on March 25, 1933, with a complaint of swelling of the legs and face of four months' duration. The family history was unimportant. The patient was married fourteen years before, and was separated from her husband after four years. The husband was living and well. There was one daughter, aged 12, and there had been no miscarriages. The social history was not remarkable. The patient's habits were regular.

The patient was born in Boston, and had lived all her life either in Boston or in Nova Scotia. She had chickenpox, measles, mumps and pertussis during childhood and scarlet fever at the age of 15. Otherwise, she had had no diseases. Ten

⁶ Myers, W K, and Taylor, F H L. Hypoproteinemia Probably Due to Deficient Formation of Plasma Proteins, J A M A **101** 198 (July 15) 1933.

years previously the patient was said to have been operated on at the Victoria General Hospital, Halifax, for appendicitis, which was characterized by pain in the right lower quadrant and vomiting. There was no incision near McBurney's point, however. She remained in the hospital for three months, two operations being done, the first an exploration. The patient did not know what organs were removed if any. The menstrual periods continued.

The patient came to Boston from Nova Scotia in October 1932. She was well until the first part of December. At this time she had a cold in the head, characterized by coughing and sneezing. Since then colds in the head had recurred at frequent intervals, and in the middle of February, following a particularly severe cold, pus drained from the left ear and continued until admission. One month following the first cold, in December 1932, the patient first noticed swelling of the eyelids and puffiness under the eyes, more marked in the morning. The swelling was practically confined to the face. Some weeks later her ankles swelled slightly. In the latter part of January and early February, the edema became quite marked. In the middle of February she was ill for three days with grip, and it was at this time that sudden severe pain developed in the left ear which was relieved by spontaneous rupture of the drum. One week before admission she was given a diet of nothing but 1 quart (236.5 cm.) of milk daily. The patient had no pains in the muscles or joints and no cramps. She had had no menstrual period since the previous November. There was no history of oliguria. She noticed a slight bloody tinge to the urine for one or two days at the time of onset of the otitis media. There had been no vomiting or headaches.

Physical Examination—The fundi were normal. The patient could not hear a watch in the left ear and a slight creamy discharge drained from the ear. The canal contained moist material. The lower posterior quadrant of the tympanic membrane was absent, and this was the source of the pus. The heart was normal. The blood pressure was 124 systolic and 78 diastolic. There was dulness over the lower portion of both lungs, with absence of breath sounds over the dull area. The white blood cell count was 13,800, of which 64 per cent were lymphocytes and 34 per cent polymorphonuclears. The hemoglobin content was 102 per cent (Sahli), and the red blood cell count was 5,100,000. A blood smear showed unusual forms of cells and 9 per cent eosinophilia. Multiple myeloma was considered. The absence of anemia and definite young forms were against the diagnosis of leukemia. Eosinophilia and lymphocytosis suggested an infection from which the patient had recovered. The urine showed a low specific gravity, no albumin and no casts. The pelvic examination revealed nothing remarkable. The temperature was normal. The basal metabolic rate was plus 15 per cent. The excretion of phenolsulphonphthalein was 78 per cent in two hours and ten minutes. The two hour renal test (Volhard and Fahr) showed the specific gravity to vary from 1.024 to 1.028.

Course—On March 29, there was an evening rise of temperature to 101 F., but on physical examination there was no change except for redness of the throat and large, red swollen tonsils, spotted with exudate. The urine showed no Bence-Jones protein, but at one time a cloud appeared after the heat and acetic acid-albumin test had been allowed to stand for ten minutes.

By April 6 the temperature was normal. The blood pressure remained low. On April 20 the edema was the same. Her condition remained essentially unchanged. On May 14, salyrgan was given as a diuretic. This was satisfactory at first, but later failed to produce diuresis. Theobromine produced no diuresis. On June 15, two teeth were extracted. About this time marked capillary relaxation was noted as shown by the dark blue cyanosis that appeared in the legs when she hung them over the edge of the bed. Until July 9, digitalization was tried.

The blood pressure remained low, ranging between 88 and 110 systolic. The ordinary cutaneous tests with protein failed to produce a reaction on July 12. On two occasions 850 cc of straw-colored fluid was aspirated from the right side of the chest. On July 15, pelvic examination showed a firm mass reaching almost to the umbilicus, but this could account for only the edema of the lower extremities. The patient's tonsils were removed on July 19. At no time was there anemia or leukocytosis above 15,000. The pelvic mass was believed to be inflammatory, and surgical exploration was probably indicated.

At the time of writing this report the patient was still in the hospital.

SUMMARY

1 A patient with nonnephritic and noncardiac edema was studied in the same manner as the patients with Bright's disease.

2 The behavior of the excretion of sulphur was the exact reverse of that found in patients with the nephrosis syndrome.

3 The nitrogen balance was evidently well maintained in this patient.

4 The excretion of sodium chloride may be taken to indicate that the diuresis produced by urea in this patient came from within the cells.

5 This report is included in the series so that these patients may be contrasted with those exhibiting the nephrosis syndrome and as a control to show that the metabolic reactions of patients with renal edema are not necessarily due to the edema per se.

ARTERIAL ELASTICITY IN MAN IN RELATION TO AGE AS EVALUATED BY THE PULSE WAVE VELOCITY METHOD

PHILLIP HALLOCK, M D

MINNEAPOLIS

The mounting incidence of deaths as a result of cardiovascular disease has stimulated investigators to inquire intensively into the nature and progress of the degenerative diseases of the heart and blood vessels, in an attempt to uncover possible etiologic factors and obtain data and methods for prediction in individual cases. A high percentage of all cardiovascular disease is associated with a hardening of the arteries or arteriosclerosis. The etiology of arteriosclerosis remains shrouded in mystery. Its recognition in the living subject has met with only a fair degree of success. By means of the electrocardiograph disease of the coronary arteries can be detected fairly early in many cases. Changes in the arteriolar system which plays such an important rôle in the regulation of arterial blood pressure may be detected in the retinal vessels with the ophthalmoscope. Then by physical examination it is possible to judge in a rather rough and approximate fashion an advanced degree of sclerosis and thickening of the medium-sized vessels, such as the radial and brachial arteries. The latter method of investigation is admittedly inadequate for the finer and more exact evaluation of the condition of the arterial wall. It is for this reason therefore, that I resorted to a method which affords quantitative data regarding arterial elasticity through physical measurements. The validity of the method, which is based on the theory of wave transmission through elastic tubular structures, has been well established by experimental procedures. The method which will be described is well applicable to a study of the rigidity of the arterial tubing in the descending aorta and in the brachioradial systems.

THEORETICAL CONSIDERATIONS OF ARTERIAL ELASTICITY

It is now recognized that the extensibility of an artery can be measured by the velocity of the pulse wave propagated through it. Moens,¹ in 1878, by experimental methods, derived the mathematical expression (1) $V = K \sqrt{\frac{r}{d}}$ for the velocity of the front of the pulse wave occurring in arteries, in which the velocity of the pulse wave (V)

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1 Moens, A. I. Die Pulskurve, Leiden E. J. Brill, 1878 p. 90

varies directly as the square root of the product gravity (g), the elasticity coefficient (E) and the thickness of the arterial wall (a), and inversely as the product of the square root of the density of the blood (D) and the diameter of the lumen of the vessel at the end of diastole (d). D may be assumed to be constant and equal to 1.055, K is a constant. Moens proved the validity of his formula by experiments on elastic tubing.

It is obvious that for practical purposes Moens' expression is of little value, as the factors E , a and d are immeasurable quantities in situ. Bramwell and Hill,² after careful consideration of the theory of wave transmission, came to the conclusion that within limits of experimental error, Moens' formula would be applicable provided the factors could in some manner be transformed into measurable units. To accommodate factors which may be measured, they ingeniously transformed Moens' formula into the following:

(2) $V = 0.357 \sqrt{\frac{v}{dv/dp}}$ or $V = 0.357 \sqrt{v \frac{dp}{dv}}$, in which $\frac{dv}{dp} \cdot \frac{1}{v}$ is the relative increase in volume (v) of the artery per millimeter of mercury increase of pressure (p). Converting this expression into a slightly different form (reciprocal), the ratio of pressure increase to volume increase ($\frac{dp}{dv} v$) has been designated as the coefficient of volume elasticity. It increases directly as the rigidity and inversely as the extensibility of the arterial wall.

Converting equation (2) into terms of percentages, it becomes

$$(3) V = \frac{3.57}{\sqrt{\text{percentage increase in volume per millimeter of mercury increase of pressure}}}$$

or (4) $\text{percentage increase in volume per millimeter of mercury rise in pressure} = \frac{12.7}{(\text{velocity in meters per second})^2}$

From expression (3) or (4) it is obvious that the velocity of the pulse wave is a function of arterial rigidity or the coefficient of volume elasticity. To determine the arterial rigidity in situ, then, it is not necessary to know the thickness of the arterial wall, its radius or the elastic coefficient E . By simply determining the rate of transmission of the pulse wave, the volume increase per unit rise of pressure (the coefficient of extensibility of vessels) can be determined in absolute units.

FACTORS MODIFYING THE VELOCITY OF THE PULSE WAVE

The velocity with which the pulse wave is transmitted is dependent primarily on the coefficient of elasticity or rigidity of the artery. However, several other factors deserve consideration. The velocity of the blood flow may be regarded as a small quantity in calculating the

² Bramwell, J. C. and Hill, A. V. The Velocity of the Pulse Wave in Man, *Proc. Roy. Soc., London*, s B 93 229, 1922.

velocity of pulse waves Yet it may affect to a noticeable degree the form of the pulse wave as well as its rate of propagation Assuming 0.75 meter per second to be the average maximum velocity of the flow of blood in the human aorta under basal conditions and 0.25 meter per second the average velocity in the carotid artery, it is obvious that the correction for the velocity of blood flow itself is small But Bramwell and Hill² pointed out that any considerable increase in the velocity of the blood as a result of local or general disturbances will cause an equal increase in the velocity of the pulse wave They stated that "any experimentally determined wave (pulse) velocity must represent the velocity of the wave relative to the blood, plus the velocity of the blood in the artery"

Another factor that may modify the velocity of the pulse wave is the act of respiration Hickson and McSwiney³ showed that the velocity of the pulse wave is slightly higher during the phase of expiration, owing to the fact that during the expiratory phase the blood pressure is slightly increased

But the chief factors concerned in altering the velocity of pulse waves are variations in the arterial elasticity The variations are essentially the result of two factors (1) the effective internal pressure within the artery, and (2) the constitution or "make-up" of the arterial wall

In regard to the former, considerable experimental evidence indicates that the pressure inside the vessel plays an important rôle in modifying the arterial elasticity and thus in modifying the speed of transmission of the pulse wave Roy,⁴ in 1880, pointed out by means of a series of extensibility curves obtained by experimental methods that the elasticity of isolated human and animal aortas depends to a large extent on the intra-arterial pressure Grunmach,⁵ in 1885, measured the velocity of the pulse waves in an attempt to establish the relationship between the velocity of the pulse wave and the aortic pressure He found that patients suffering from defects of the aortic valves and severe anemia, both of which conditions give rise to low aortic pressure, had slow velocities of the pulse waves, while those suffering from arteriosclerosis had high velocities, a fact which he attributed to increased aortic pressure

Bramwell and Hill,² in 1922, after recalculating Roy's curves were able to derive from them the percentage increase in volume of the

3 Hickson, S. K., and McSwiney, B. A. Effect of Respiratory Movements on Pulse Wave Velocity, *J. Physiol.* 59: 217, 1924

4 Roy, C. S. The Elastic Properties of the Arterial Wall, *J. Physiol.* 3: 125, 1880-1882

5 Grunmach, E. On the Pulse Velocity in Diseases of the Circulatory Apparatus, *Virchows Arch. f. path. Anat.* 102: 565, 1885

vessel per millimeter of mercury increase in pressure and thus the velocity of the pulse wave at various pressures. Their results showed that the velocity of the pulse wave was low at low pressures and increased considerably at higher pressures. By an ingenious method, the same investigators experimentally confirmed these deductions elicited from Roy's curves by direct mechanical measurement of the velocity of the pulse wave in isolated arteries which were filled with mercury in order to slow the transmission of the wave. They found that at a diastolic pressure of 25 mm of mercury the velocity of the pulse wave was 3.76 meters per second. At a diastolic pressure of 200 mm of mercury, it increased to 18.5 meters per second. Their results indicated conclusively that the velocity of the pulse wave increased almost directly as the blood pressure, and that the rate of propagation of the pulse wave was a mechanical phenomenon depending on the elastic properties of the vessels. Thus, with increasing diastolic pressure there appeared to be a gradual diminution of extensibility and a gradual increase of rigidity.

Bramwell, McDowall and McSwiney,⁶ in 1922, described a method by which the extensibility of the brachioradial artery could be measured at all internal pressures from zero up to the diastolic pressure in living man. By the employment of a compression bandage they were able to alter at will the effective pressure inside a certain region of an artery and to calculate the velocity of the pulse wave in the segment of artery submitted to the various pressures. Making use of the formula

$$V = \frac{d}{y-x} \frac{1}{\frac{(1-d)}{1}}$$

in which x equals the transmission time between two points at a distance (1) from each other and y the time between the same points when a bandage of length d is applied, the velocities of the pulse wave at various diastolic pressures were calculated. They found that the velocity of the pulse wave increased and therefore extensibility decreased as the intra-arterial pressure was increased.

Bramwell, Downing and Hill,⁷ in 1923, by the use of the two hot-wire sphygmographs and two strings of an Einthoven galvanometer, repeated their study on isolated arteries in order to arrive at more accurate measurements. This study was limited to the carotid artery, a vessel which contains only a relatively small amount of muscular tissue. In twelve observations, the velocities were recorded at twelve different pressures ranging from 15 to 250 mm of mercury. Convert-

6 Bramwell, J. C., McDowall, R. J. S., and McSwiney, B. A. The Variation of the Arterial Elasticity with Blood Pressure in Man, *Proc. Roy. Soc., London*, s. B **94** 450, 1923.

7 Bramwell, J. C., Downing, A. C., and Hill, A. V. The Effect of Blood Pressure on the Extensibility of the Human Artery, *Heart* **10** 289, 1923.

ing formula (3) into another convenient form, the velocity of the pulse wave may be expressed in terms of millimeters of mercury rise of pressure per 1 per cent increase of volume or rigidity of the artery as follows

$$(5) V = 3.57 \sqrt{\frac{\text{millimeters of mercury of pressure required to produce 1 per cent increase in volume}}{\text{increase in volume}}}$$

After calculating the rigidity of the vessel from the experimentally determined velocity of the pulse wave by means of this formula, they plotted the various blood pressures against rigidity, and were able to demonstrate a striking increase of rigidity of a vessel with the increase of blood pressure. The evidence proves that the arterial elasticity depends to a considerable extent on the diastolic blood pressure.

The second important factor modifying the rate of transmission of the pulse wave is concerned with changes inherent in the arterial wall. According to the classic formula of Moens,¹ the velocity of the pulse wave varies directly as the square root of the thickness of the arterial wall and inversely as the square root of its diameter. Consequently, any factor which causes thickening of the wall of the artery or narrowing of its lumen will increase the rate of transmission of the pulse wave.

Bazett and Dyer,⁸ in 1922, showed that the velocity of transmission is considerably lower in the large vessels than in the smaller peripheral ones. This observation has been confirmed in my studies on the transmission time of the pulse wave through the aorta and brachioradial vessels. The fact that medium-sized arteries, such as the radial, the brachial or the carotid vessels, are endowed with relatively more muscular tissue than the aorta and the iliac vessels, and the fact that the internal diameter of the peripheral arteries is considerably less than that of the aorta and its immediate branches probably explain the difference in the rates of transmission of the pulse wave in these vessels. Furthermore, because of these anatomic variations, it is reasonable to assume that the medium-sized arteries, as opposed to the large vessels, are subjected to greater vasomotor influences, which may functionally or otherwise so alter the tonus and degree of contraction of their walls as to increase the volume elastic coefficient (rigidity) and consequently the speed of the pulse wave.

Laubry, Mougeot and Giroux,⁹ in 1921, by increasing the tonicity of the artery in situ by cold applications showed that the velocity of the pulse wave increased. On the contrary, vasodilatation diminished the speed of the pulse wave.

8 Bazett, R. C., and Dyer, N. B. Measurement of Pulse Wave Velocity, *Am J Physiol* **63** 94, 1922.

9 Laubry, C. H., Mougeot, A., and Giroux, R. The Speed of the Arterial Pulse Wave, *Arch mal du cœur* **14** 49, 1921.

MacWilliam,¹⁰ in 1902, showed that medium-sized vessels such as the carotid, obtained soon after the death of the animal, could be submitted to various states of relaxation and contraction by various physical and chemical means. By an ingenious method he measured the increase in volume of short segments of the altered vessels under various degrees of pressure, and then plotted volume-elasticity curves in which the volume was plotted along the ordinate axis and the pressure along the abscissa. The curve of the strongly contracted vessel was concave to the abscissa, while that of the relaxed vessel was convex to the abscissa. He concluded that the differences in the shape of the curves were due to the fact that the muscular resistance of the contracted vessels opposed extensibility at normal internal pressures, while in the relaxed vessels the muscular contraction was lacking to a considerable extent and thereby favored extensibility at the same normal internal pressures.

MacCordick¹¹ found that the carotid arteries of the horse were contractile several days following removal and that the various degrees of contraction made a decided difference in the measurements of elasticity. Renterwall¹² found that when extension curves were plotted by testing the same artery in rapid succession, a difference was found between the successive curves. By treating the same arteries with epinephrine he was able to modify the shape of the curves. He concluded that the differences in the curves were due to the varying degrees of contraction. These experiments show that the transmission of the pulse wave in medium-sized vessels is affected to a considerable extent by the degree of muscular contraction as well as by the intra-arterial pressure. Friberger,¹³ in 1912, studied the velocity of the pulse waves in arteries with palpable thickening of the walls (in patients suffering from nephritis) and attributed the increase of the velocity of the pulse wave to the increased muscular tension combined with degenerative changes in the arterial wall. Sands,¹⁴ in 1925, was unable to confirm this observation.

The constitution of the wall of the aorta is such that its physical behavior is different from that of the medium-sized vessels. While there is a slight amount of smooth muscle in the aortic wall, this has a negligible effect as far as the transmission of the pulse wave is con-

10 MacWilliam, J. A. On the Properties of the Arterial and Venous Walls. *Proc. Roy. Soc., London* **70** 109, 1902.

11 MacCordick, A. H. Ueber die Stromung des Blutes in der Gefassbahn und die Spannung der Gefasswand, *Beitr. z. path. Anat. u. z. allg. Path.* **66** 377, 1920.

12 Renterwall, quoted by Thoma, R. Ueber die Elastizitat der Arterien und die Angiomalacia, *Virchows Arch. f. path. Anat.* **236** 242, 1922.

13 Friberger, R. Ueber die Pulswellengeschwindigkeit bei Arterien mit fühlbarer Wandverdickung, *Deutsches Arch. f. klin. Med.* **97** 280, 1912.

14 Sands, J. Studies in Pulse Velocity. Pulse Wave Velocity in Pathological Conditions, *Am. J. Physiol.* **71** 519, 1925.

cerned Thus, Zon,¹⁵ in 1932, experimentally, in rapid succession, obtained extension curves of a strip of ascending aorta and found no difference between the respective curves After the application of a 0.005 per cent solution of epinephrine (surrounding the aorta) he repeated the experiments and found no appreciable change in the form of the curve

The elastic properties of the aorta are governed essentially by the diastolic pressure and by the amount of elastic tissue contained in its wall The aorta is probably almost entirely devoid of vasomotor influences such as control the medium-sized and smaller arteries Physical tests, to be described later, show that the extensibility of the aorta is considerably greater than that of the medium-sized vessels This is undoubtedly due to the fact that the aorta, as indicated by the Weigert and Van Gieson stains contains a much greater amount of elastic tissue The fact that the lumen of the aorta is greater than that of the medium-sized vessels also explains in part its increased extensibility

The arterial changes that occur with age have thrown considerable light on the physical properties of the aortic wall Frank,¹⁶ in 1927 showed that the elastic volume coefficient (rigidity) is dependent on the tension per unit cross-section area of the vessel, approximately as given by the equation $E = E_0 + qt$,² in which E denotes the elastic coefficient, E_0 the residual elasticity, q the elastic characteristic according to age and t the tension He found that the value q changed in the individual arteries much more than E_0 , and also that q increased with age Thus, in old people he found the value of q to be six times as great as that found in children, while E_0 remained approximately the same With a tension of zero, E remained the same for both longitudinal and transverse expansion With increasing tension the former increased more rapidly than the latter Thus the extensibility of the aorta is much greater in the longitudinal direction than in the transverse He concluded, therefore, that the elastic substance in the arterial wall could not be homogeneous He stated that some colloidal alterations in the arteries are responsible for changes in the elasticity relations He also pointed out that arterial rigidity increased very little with increased tension at lower tensions in young persons On the other hand, in older subjects the arterial rigidity increases rapidly with an increase in tension at lower tensions, so that the curves assume almost straight lines at their very beginning

It appears from recent work that the alterations that occur with age, especially in the aorta, involve corresponding regressive changes in the

15 Zon, L., Unpublished material (Thesis, University of Minnesota, 1932)

16 Frank, O. Das Altern der Arterien, Sitzungsber d Gesellsch f Morphol u Physiol **37** 23, 1927, abstr, Ber u d ges Physiol u exper Pharmacol **41** 234, 1927

elastic tissue Aschoff¹⁷ called attention to the fact that when an aorta was loosened from its attachments from the vertebral column, except at its ends, and then cut transversely through its midportion, the cut ends would retract considerably in young people, but not to any appreciable extent in old persons This difference he attributed to weakening of the elastic tissue With advancing age the size of the aorta gradually increases, and physical tests indicate that extensibility decreases Zon,¹⁸ in an attempt to correlate the physical behavior of aortas at various ages with their respective histologic structures, determined the extensibility of rings of aortas from all periods of life His studies show a progressive disappearance of elastic tissue, with a slight replacement by collagenous tissue and a change in form of the elastic fibers with age He expressed the belief that the decrease of extensibility with age is due to the degeneration of elastic tissue

It is obvious from the preceding considerations that the factors which govern the transmission of the pulse waves in medium-sized vessels are not altogether similar to those that govern the transmission of pulse waves in aortas

A number of investigators have studied the rate of transmission of the pulse wave in man, especially in the medium-sized vessels such as the radial, brachial and carotid arteries Several have even attempted to study the rate of transmission through the aorta and the iliac vessels These investigations have afforded valuable information concerning the elasticity of arteries However, although the results indicate that there is a progressive increase of velocity with age, an inspection of the values for the velocity of the pulse wave, as reported, reveals considerable discrepancy as to what constitutes the norms of velocity for different age groups Furthermore, the increments of the velocity of the pulse wave reported in successive age groups are of such variable magnitude as to preclude the possibility of establishing a normal standard A glance at Wiggers' ¹⁹ table (1923), derived from the graphic records of normal adults, as given by various investigators, shows the variability of the values reported

Obviously such conflicting results are of little value in attempting to establish a normal range of velocities of the pulse wave The disparity shown in the results can be explained only in part by the difference in methods and technics employed in registering the rate of transmission of the pulse wave However, since the introduction of the segment capsule by Frank,¹⁹ in 1913, and the hot wire sphygmograph by Hill,²⁰

17 Aschoff, L Lectures on Pathology, New York, Paul B Hoeber, Inc, 1924, p 131

18 Wiggers, C J Modern Aspects of Circulation in Health and Disease, ed 2, Philadelphia, Lea & Febiger, 1923

19 Frank, O Theory of Segment Capsule, *Ztschr f Biol* **59** 526, 1913

20 Hill, A V Hot Wire Sphygmograph, *J Physiol* **54** Cxvii, 1920-1921

in 1920, accurate optical records of the pulse wave can be obtained, thus minimizing errors that otherwise would be present. Another source of error that may account for the inconstancy of results is the variability in the methods of measuring the anatomic landmarks which represent the actual arterial distance traversed by the pulse wave in passing from the heart to points at which the pulse wave excursions are recorded. Moreover, in older persons the tortuosity of the vessels introduces an immeasurable though probably not great error.

Recently, Hemingway, McSwiney and Allison,²¹ employing the hot wire sphygmograph, showed by accurate measurements that the veloci-

TABLE 1—*Values for the Velocity of the Pulse Wave Reported in the Literature**

Year	Investigator	Carotid Radial Velocity, Min and Sec	Aortic Velocity, Min and Sec
1864	Oacrmak	67	
1878	Moens ¹	87	
1879	Grunmach ²	820	
1887	Keyt	737	
1889	Edgren	763 to 732	
1889	Horweg	90	
1912	Munzer	90 to 12	
1912	Friberger ¹³	67 to 94 (men) 70 to 100 (women) (16 to 36 years)	
1912	Rusebke	90	
1921	Laubry, Mougeot and Giroux ⁶	80	
1922	Bramwell and Hill ²	59 to 75 (15 to 50 years)	
1922	Bazett and Dryer ⁸	52 to 79 (13 to 38 years)	45 to 97
1924	Sands ¹⁴	362 to 695 (16 to 41 years)	357 to 369
1927	Beyerholm	591 to 735 (1½ to 60 years and more)	
1932	Hafkesbring and Ashman	58 to 103 (17 to 44 years)	

* Table 1 is in part copied from Wigger ¹⁸. I have added to Wigger's table the last four authors and the values for the velocities of pulse waves they obtained.

ties of the pulse wave and the extensibilities of the brachial and radial arteries varied considerably in normal persons, thus further complicating the problem of arterial elasticity. They found after the construction of a series of curves relating the velocity of the pulse wave and extensibility to effective arterial pressures, that the arteries of normal subjects could be classified in three types: (1) normal, (2) hyperextensible and (3) hypo-extensible. They stated that while Bramwell, Hill and McSwiney ²² found the coefficient of the mean extensibility of an artery

21 Hemingway, A., McSwiney, B. A., and Allison, P. R. Extensibility of Human Arteries, *Quart J Med* **21** 489, 1928.

22 Bramwell, J. C., Hill, A. V., and McSwiney, B. A. The Velocity of the Pulse Wave in Man in Relation to Age as Measured by the Hot-Wire Sphygmograph, *Heart* **10** 233, 1923.

at the age of 20 to be 0.33, in the experiments of Hemingway, McSwiney and Allison, the variation at this age was between 0.3 and 0.64. Hemingway, McSwiney and Allison attributed this wide variation to influences originating presumably from the vasomotor center and affecting the tone of the smooth muscle in the arterial wall.

It is apparent from the preceding considerations that the status of data on the velocity of the pulse wave, as far as the practical application for evaluating arterial elasticity is concerned, is attended by considerable disagreement and confusion. It is necessary, first, to establish criteria for normal standards of the velocity of the pulse wave at various ages. Once these are established it will be possible to evaluate the elasticity of the vessels in which arterial disease is suspected. Such an object can be accomplished only by the use of a precise and accurate recording instrument with which the velocity of the pulse wave of a large series of patients of all ages can be measured. After the data are obtained it is necessary to determine the normal values for each age group. If the observers mentioned previously are correct in stating that the elasticity of the vessels of normal persons falls into one of three groups, then it is necessary to determine the limits of variability of arterial elasticity in each age group. If, moreover, there is a relationship between the elasticity and diastolic pressure, it is necessary to subject this relationship to a quantitative analysis by statistical means.

METHOD

Registration—In this work, optical registration was employed throughout. An optical projection system, as described by Wiggers¹⁸ for reflecting light from two segment capsules, was used in such a manner that the illuminating beam of light was thrown through two adjustable vertical slits onto small rectangular mirrors (1 by 4 by 0.01 mm) mounted on the margin of segment capsules. A time marker activated by a motor synchronized by a tuning fork was interposed between the condensing lens and the adjustable slots at the focal point of the light for recording the periods of time in fifths of a second. A narrow hood 0.75 meter long was placed between the recording camera and the segment capsules, and the apparatus was carefully aligned before each operation to obviate parallax. The segment capsules were connected to the receiving instruments by tubing as short as possible and of exactly the same length in the two systems, thus assuring equal transmission time of the pressure waves traveling in the receiving systems. The receiving apparatus consisted of two parts, a shallow aluminum cup being used over the carotid vessels and a glycerin pelote over the radial and femoral arteries. Segment capsules 12 mm in diameter were employed.

Measurement of Records—The beams of light reflected from the segment capsules were directed on the cylinder lens of a Hinde photokymograph and recorded on sensitized bromide paper, 12 cm wide. Each record contained two sets of curves, the first recording the pulse waves from the radial and from the carotid arteries taken simultaneously, and the second recording similarly the pulse waves from points on the carotid and on the iliac arteries. The first set of curves determines the brachioradial transmission time, the second set determines the

aortic-iliac transmission time Each curve consists of from six to eight cycles Of these, the four or five cycles showing the most abrupt upstrokes were measured, and an average figured Differences in measurements of the various cycles did not vary as a rule more than 3 or 4 per cent

The averages of four or five cycles were figured to obtain a mean value The variations in the individual readings were partially due to changes in blood pressure associated with respiratory movements Because of the four or five successive readings on each subject, it was possible to test the reliability of the technic (table 2) The mean and total range of the deviations from the mean of the four or five readings were calculated for twenty-five subjects chosen at random from each age group, except in the age group from 5 to 9 years, in which nineteen records were chosen and in the 65 year age group, in which eighteen records were chosen

TABLE 2—*Deviations of the Instrumental Units*

Age Period, Years	Mean Deviation of Five Readings		Total Range of Deviation of Five Readings	
	Maximum	Mean	Maximum	Mean
	Velocity of the Radial Pulse Waves			
5 to 9	0.28	0.12	0.7	0.4
10 to 14	0.30	0.15	0.9	0.4
15 to 19	0.26	0.13	1.0	0.4
20 to 24	0.35	0.14	1.0	0.4
25 to 34	0.24	0.11	0.8	0.4
35 to 44	0.26	0.15	0.7	0.4
45 to 54	0.20	0.14	0.8	0.4
55 to 64	0.28	0.14	0.8	0.4
65 and more	0.25	0.13	0.9	0.4
Average	0.28	0.13	0.87	0.4
Velocity of the Aortic Pulse Waves				
5 to 9	0.32	0.13	0.8	0.4
10 to 14	0.30	0.12	1.0	0.4
15 to 19	0.23	0.12	0.6	0.4
20 to 24	0.35	0.15	1.2	0.4
25 to 34	0.23	0.13	0.8	0.4
35 to 44	0.28	0.14	0.8	0.4
45 to 54	0.23	0.13	0.8	0.4
55 to 64	0.36	0.15	1.0	0.4
65 and more	0.37	0.17	0.9	0.4
Average	0.30	0.14	0.88	0.4

According to Tippet²³ the standard deviation, σ , may be determined from the mean range for the twenty-five sets of five readings each by dividing the mean range by a constant, 2.326 thus $\sigma = \frac{0.4}{2.326} = 0.17$, when the constant is obtained from the tables according to the number of readings in each sample in the series Since the mean range was the same for all age periods and for both radial and aortic velocity, the standard deviation is the same, namely, 0.17 Since the mean deviations for both groups vary only from 0.11 to 0.17, the coefficients of variation, $C V = \frac{\sigma}{\text{mean}} \times 100$, for all age periods and for velocities of both aortic and radial pulse waves are between 1 and 15 per cent Hence, by definition of the standard deviation and the coefficient of variation, two thirds of the time the error of the instrument would be within a range of from ± 1 to ± 15 per cent ($\pm 1 C V$) and 95 per cent of the time within a range from 2 to 3 per

23 Tippet, L. H. C. Method of Statistics, London, William Norgate, Ltd., 1931, p. 26

cent Hence, the probable range of error introduced into the readings of the velocity of aortic and radial pulse waves is about 25 per cent

In some of the records the exact beginning of the systolic upstroke was complicated by the presence of a presphygmic vibration (period of rising tension of the ventricular systole) In these cases the records were rejected because of the difficulty in determining the exact beginning of the upstroke

The records were measured by means of a glass reading plate having one face accurately etched in millimeters The etched face was laid down directly on the record so as to avoid parallax Both the reading plate and the record were placed on a stage to which was attached an adjustable microscopic lens capable of magnifying the record six times In this manner the distance could be measured to within 0.1 mm With the sensitized paper traveling at the rate of 100 mm per second, the intervals of time can be read to within one thousandth of a second In many of the records, the commencement of the upstroke was marked with a fine-pointed needle held under a microscopic lens, thus insuring accuracy

All records were recorded with the patient lying at ease in the supine position In measuring the brachioradial velocity an aluminum cup was held snugly over the bifurcation of the right carotid artery, while the glycerin pelotte was fixed firmly over the radial vessel of the right wrist by a strap encircling the wrist In measuring the aortic time of transmission, the aluminum cup was held firmly on the left carotid bifurcation, and the glycerin pelotte was held firmly over the iliac artery just below the inguinal ligament When the patient was excited and the pulse rapid, he was given a five minute period of rest before the receiving apparatus was applied The blood pressure was measured by the auscultatory method after taking the record In most cases, the height and weight were also recorded

Anatomic Landmarks and Measurements—As mentioned previously, the anatomic measurements may introduce a considerable error if not taken with precision Thus, assuming the total distance measured to be about 50 cm, a difference of 2 cm in measurement would introduce an error of 4 per cent If the pulse wave traverses an actual distance of 50 cm in six-hundredths of a second, the velocity would be 8.33 meters per second, while if the measured distance was 48 cm, the velocity would be determined as 8 meters per second

All patients were made to assume as nearly as possible the same position, so that the anatomic landmarks could easily be recognized and accurate measurements taken therefrom The landmarks of the bifurcation of the common carotid artery can be found by following the superior border of the lamina of the thyroid cartilage out to its very end At this point the bifurcation can most easily be palpated Because of the anatomic relationships in the neck, it is important that the head be only slightly extended Excessive extension may introduce an error in measurement

The measurements of transmission time for the carotid and radial vessels were all made on the right side of the body Accurate measurement from the origin of the right subclavian artery to the radial artery at the styloid process can be made by extending the right arm at right angles to the long axis of the body The length of the subclavian brachioradial branch can be determined accurately by measuring the direct distance from the sternoclavicular joint to the styloid process of the radius Likewise, if the head is not thrown back too far, the carotid vessel can be mapped out with precision from the same point over the sternoclavicular joint directly to its bifurcation Similarly the length of the left common carotid artery can be measured

To obtain the transmission time of the pulse wave through the aorta, it was necessary to make a correction for the aortic arch. The origin of the left common carotid artery as topographic anatomic sections show, and as I have observed in a large number of postmortem examinations, is at the level of the inferior border of the first left rib just lateral to the midsternal line. The lower border of the first left rib at its junction with the sternum was therefore used as a landmark. The level of the crests of the ilium at the midline of the body was taken as the landmark for the bifurcation of the aorta. The direct distance from the lower border of the first rib to the midpoint of a line passing over the iliac crests was measured. To this distance was added the length of the iliac artery. Its length was determined by measuring the direct distance from the midline of the abdomen at the level of the iliac crests to the inguinal ligament at which point the glycerin pelotte lay over the iliac artery just at its entrance into the femoral canal.

To make this correction for the arch, 4 cm. was added to the measurements in persons over 15 years of age, and 2 cm. was added to those of subjects under 15 years. These correction values were obtained from the study of eighty-three postmortem examinations of persons ranging from 3 to 99 years of age. The external measurement of the length of the aorta was first made, as already described. After opening the thorax and abdomen, the aorta was carefully cleaned, and the distance from the origin of the left common carotid artery to the bifurcation of the aorta was measured with a piece of string laid carefully along the intima of the aorta. In forty-seven cases both the greater and the lesser curvatures of the aorta were measured, and the mean value obtained. In the remaining cases, only the greater curvature was measured. In these, when the greater curvature was measured and compared to the externally measured aortic distance, the average difference was 5.77 cm. In the forty-seven cases in which both the greater and the lesser curvature were measured and the mean computed, the average difference between the internally and the externally measured distance was 4.87 cm. The average correction factor in the patients under 15 years of age was calculated to be 1.8 cm. For convenience, the factor of 2 cm. was used as the correction factor in patients under 15 years. Any error due to the use of this factor will be less than ± 4 per cent. While the correction factor actually determined for use above the age of 15 was 4.87 cm., I have added only 4 cm., as the greater portion of the postmortem cases in which the correction factor was determined fell in the older age group, and a considerable number of these patients had died of cardiovascular and renal diseases. Any error caused by using this factor of 4 cm. will be less than ± 4 per cent in 90 per cent of all cases. In 10 per cent of the cases the error is greater than 4 per cent and may occasionally be as high as 10 per cent. In most of these cases there is considerable lengthening of the arch associated with atherosclerosis, and the external measurement cannot be expected to be as accurate as when there is no aortic lengthening. A marked deformity of the spine can also cause considerable error in this measurement.

Aortic Velocity of Transmission—This was obtained in the following manner. First, simultaneous curves were recorded from the pulses at the bifurcation of the left common carotid artery and at a point over the iliac artery at the inguinal ligament.

Second, measurements were taken of the distance from the lower border of the left first rib to landmarks on the neck and inguinal ligament (with the correction factor added to the latter) and the former measurements subtracted from the latter to obtain the distance traversed by the pulse wave in the recorded time interval. Finally, to arrive at the velocity of transmission of the pulse wave, the

distance traversed was divided by the time interval as recorded between the commencement of the carotid and that of the iliac systolic upstroke (fig 1, aortic curves)

Carotid-Radial Velocity of Transmission—In a similar manner, this was calculated (fig 1, radial curves), except that the right sternoclavicular joint was used as one of the landmarks instead of the lower level of the first left rib, and a point near the styloid process of the radius where the pelotte was fixed as the landmark instead of the midpoint on the inguinal ligament

The transmission time of the pulse waves through the aorta and iliac artery may be utilized as an accurate factor in determining the minute output of the heart from the Broemser and Ranke formula,²⁴ as the accuracy of their equation depends to a large extent on knowing the distensibility of the central vessels and the aorta

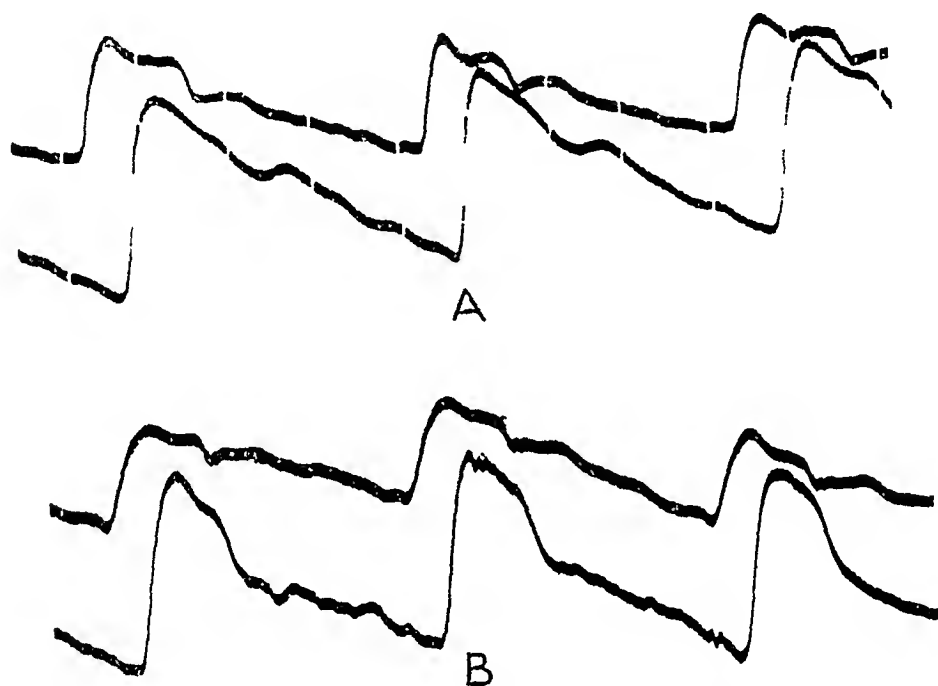


Fig 1—Examples of optically recorded tracings obtained by the segment capsule method as described in the text. In the lower record a finer time marker was employed. The time lines, however, can readily be seen under magnification. A indicates radial curves. B, aortic curves.

MATERIAL

The age group from 5 to 9 years was composed of thirty-three subjects, eighteen of whom were girls. About 85 per cent were apparently normal children who were attending school, the remaining 15 per cent were hospital patients who were convalescing from acute infections such as otitis media, acute infection of the upper respiratory tract and pyelocystitis.

The age group from 10 to 14 years was comprised of thirty-seven children, twenty-one of whom were boys. Their selection was similar to that of the previous group. Observations were made on sixty-four in the age group between 15

²⁴ Broemser, P. and Ranke, O. L. Ueber die Messung des Schlagvolumens des Herzen auf unblutigem Wege, *Ztschr. f. Biol.* 90: 467, 1930.

and 19 years, of whom twenty-three were boys. Of the twenty-three, 56 per cent fell in the age period from 15 to 17 years, and of forty-one girls, 83 per cent were 18 and 19 years of age. Uniformity between the males and females is therefore lacking in this group. Of the forty-one females, approximately 81 per cent were nurses who had just entered training. The twenty-three males were all hospital patients, most of them convalescing from herniotomies and appendectomies. Several were convalescing from lobar pneumonia and other acute infections.

The age group from 20 to 24 years comprised a hundred and twenty subjects. Thirty-five were males, all medical students. The eighty-five females were nurses. They were evenly distributed in the age period.

There were eighty-seven persons in the age group between 25 and 29 years, eighteen of whom were females. The sixty-nine males were interns, residents and senior medical students. Ninety per cent of the females were nurses, and 70 per cent of them fell in the age group from 25 to 26 years.

The age group from 30 to 39 years was comprised of seventy-seven persons, of whom seventeen were females. They were fairly well distributed throughout the ten year age period. Approximately 75 per cent were hospital and dispensary patients. They were carefully questioned and examined for the presence of cardiovascular diseases. No person suspected of having cardiovascular disease was used in this investigation. Of the 75 per cent approximately 50 per cent were patients who were being treated for peptic ulcers.

A similar situation existed in the age group from 40 to 49 years, comprising seventy-three persons. Approximately 80 per cent of these were hospital and dispensary patients. It is interesting to know that when the selection for this age group was made, a considerable number of candidates were rejected because of the presence of conditions suggesting cardiovascular involvement, such as coronary disease, hypertension and arteriosclerosis. Only 15 per cent of the persons in this group were females. The small number of females was due to the fact that a large number of the candidates were rejected on account of obesity. Obesity makes it difficult to determine accurately the length of the aortic-iliac stretch.

The same condition obtained in the age group from 50 to 59 years* with fifty-eight subjects, of whom 65 per cent were females. With few exceptions, no one with a diastolic pressure above 90 was accepted. This rule applied to all groups. Likewise, a systolic pressure of over 150 was considered a cause for rejection.

The age group from 60 to 69 years consisted of thirty-three persons of whom five were females. In the age group from 70 to 78 years only nine cases were reported, of which one was in a woman. These were also hospital and dispensary patients who appeared to be in a fairly good state of health. None had hypertension, yet all of them had definitely thickened and palpable brachial vessels. Some tortuosity of the brachial vessels was also noted. None had palpable goose-ring brachial or radial vessels. Furthermore, in all nine cases roentgenograms of the heart taken at a distance of 6 feet (182 cm) showed no definite cardiac enlargement.

The chief difficulty in selecting proper subjects from the older age groups appears to be that no method is available by which one can evaluate even approximately the condition of the brachioradial and aortic vessels. Arteriosclerosis is a common observation in people over 45 years of age, but the degree present varies considerably. Palpation is, after all, too crude a method to be employed in the selection of subjects. The pulse pressure gives one, at times, a notion of the degree of arteriosclerosis of the aorta in aged persons, although the finding of high pulse pressures in all persons (assuming, of course, aortic insufficiency to be ruled out) who have aortic arteriosclerosis is indeed inconstant. The size of the cardiac

shadow may be of some aid. This procedure was carried out in the age group from 70 to 79 years before the velocities of the pulse wave were recorded. However, if one accepts the work of Fahr and his associates,²⁵ arteriosclerosis without narrowing the lumen of the aorta presumably does not increase the work of the left ventricle, and therefore people with arteriosclerosis of the aorta, uncomplicated with other cardiovascular diseases, should not have big hearts.

While I am fully aware of the fact that the subjects selected in the older age groups, especially over 60 years may not have been altogether characteristic examples of this age group, every attempt was made to select subjects who appeared to be as normal as one is able to judge, at least as far as the cardiovascular system was concerned.

It is recognized that if measurements could be made on older persons of the higher walks of life, whose living conditions have rendered them less liable to diseases of the circulatory system and of associated diseases, a more accurate cross-section of the normal population for the particular age group might be obtained.

RESULTS AND INTERPRETATIONS -⁶

In order to demonstrate the age changes in the velocity of the pulse wave, the values of the velocities of both radial and aortic pulse waves were plotted against age, and the mean curve drawn through the series of observations. The resulting graphs (figs 2 and 3) show the age increase and dispersion or spread of the observations. The central trends of the velocity of both radial and aortic pulse waves and of the two sexes combined are illustrated by point-to-point curves drawn so as to represent the means for each age period (tables 3 and 4). The central zones of dispersion expected to enclose two thirds of the cases are drawn in according to ± 1 standard deviation (tables 6 and 7) from the mean for each age group, with the exception of the velocity of the radial pulse wave for the last age period, in which the standard error for the previous age period is projected in dotted lines. The sex differences in age trend are shown in figure 4.

The means and their standard errors for the velocity of the aortic and radial pulse waves for males, females and both sexes for each age group are given in tables 3 and 4, respectively. The standard deviations for each age period and each sex and their standard errors are given in tables 6 and 7.

With few exceptions, values for the velocity of both radial and aortic pulse waves tend to increase in successive age periods. The trend

²⁵ Fahr, G., Davis, J., Kerkhof, A., Hallock, P., and Giere, E. Hemodynamics of Arteriosclerosis, *Am J Physiol* **101** 376, 1932.

²⁶ In the following discussion, for the sake of brevity, I have purposely avoided the use of the terms "arterial elasticity" and "arterial rigidity." The velocity of pulse waves is a direct function of arterial rigidity and an inverse function of arterial elasticity. It is therefore essential that one bear in mind that the terms indicating an increase of velocity of radial and aortic pulse waves imply an increase of arterial rigidity or, conversely, a decrease of arterial elasticity.

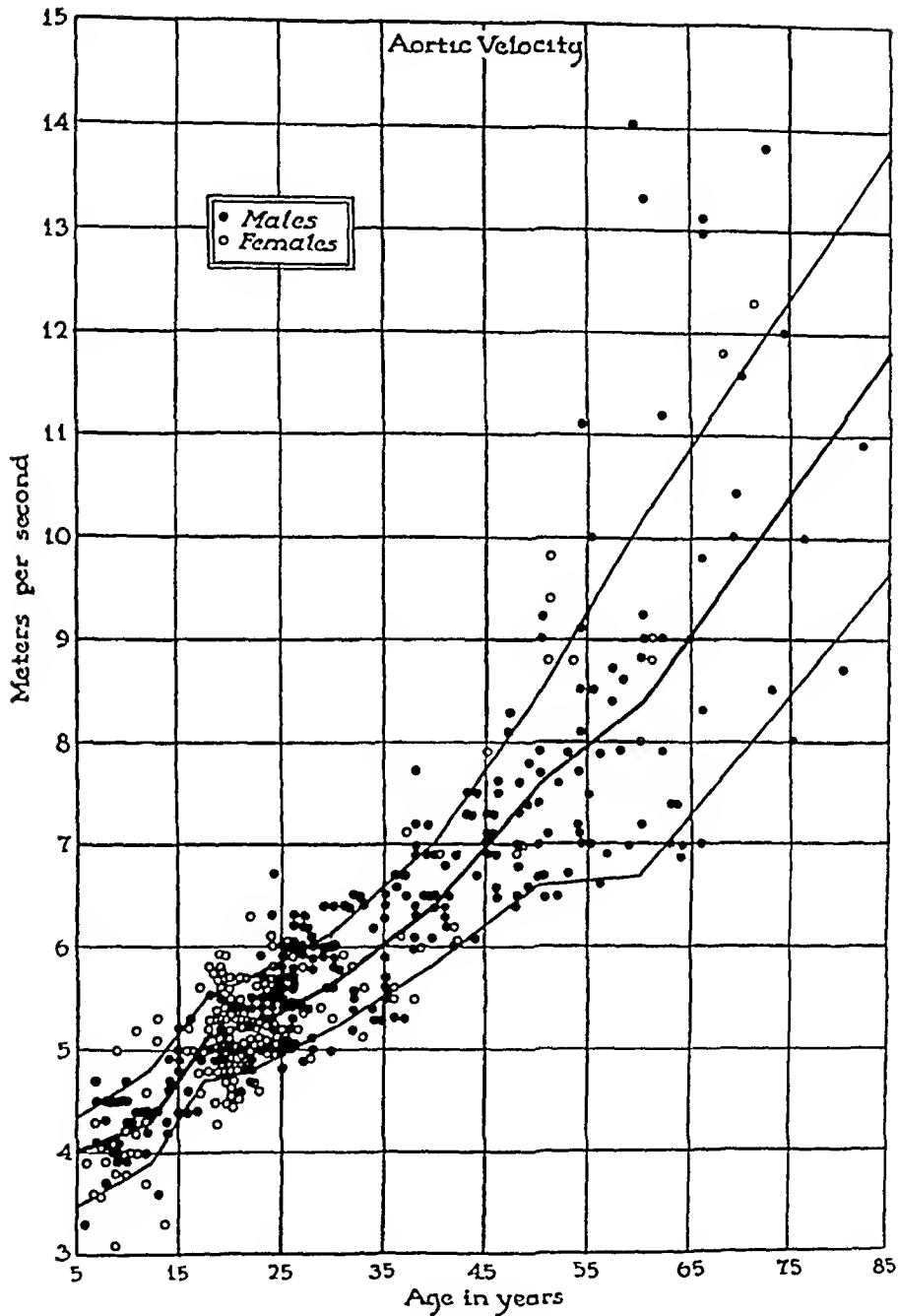


Fig 2—Graph showing the distribution of velocity of aortic pulse waves with age. The central trend is indicated by the point to point curve drawn into the mean velocities for five and ten year age intervals. The central zone of variability expected to contain two thirds of the individual observations is indicated by the point to point curves drawn into the standard deviation for each age interval.

is illustrated in figure 4. The differences between mean velocities for adjacent age groups appear significant (tables 8 and 9) when subjected to statistical analysis. The differences between the means of successive age groups are in this study usually more than 2 times their standard errors, i. e., they would occur by chance alone less than five times in a hundred.²⁷

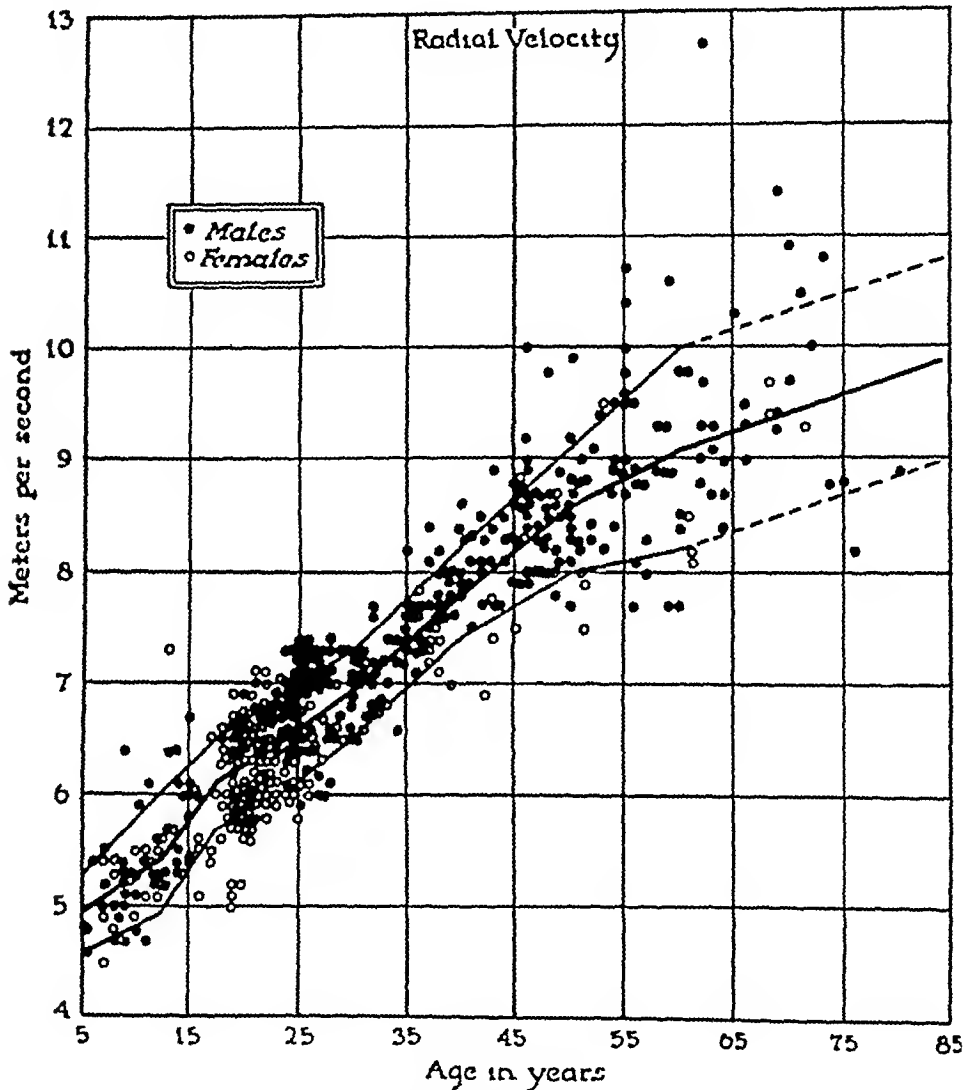


Fig 3—Graph showing the distribution of velocity of mean radial pulse waves with age. The central trend is indicated by the point to point curve drawn into the mean velocities for five and ten year age intervals. The central zone of variability expected to contain two thirds of the individual observations is indicated by the point to point curves drawn into the standard deviation for each age interval.

²⁷ In ordinary statistical practices, when a difference between two means is 2 times the standard error, the difference is considered possibly significant, since such a difference would occur by chance only five times in a hundred (Dunn, H. L. *Statistical Methods in Physiology*, *Physiol Rev* 9:275, 1929). Some biometricians consider that it is wiser to use 3 times the standard error. Then, P is 0.01, i. e., difference would occur by chance only one time in a hundred.

TABLE 3—Age Changes in the Aortic Velocity of Both Sexes (Mean Aortic Velocity and Its Standard Error)

Age, Years	Males		Females		Difference and Its Standard Error	Difference		Both Sexes	
	Number	Mean	Number	Mean		Standard Error	Probability Integral	Number	Mean
5 to 9	13	4.131 ± 0.147	11	4.000 ± 0.130	-0.131 ± 0.214	0.61	0.542	24	4.071 ± 0.090
10 to 14	17	4.311 ± 0.077	15	4.313 ± 0.117	-0.023 ± 0.166	0.17	0.865	32	4.323 ± 0.078
15 to 19	18	4.578 ± 0.091	39	5.223 ± 0.065	+0.350 ± 0.114	3.06	0.003	57	5.118 ± 0.058
20 to 24	31	5.352 ± 0.078	77	5.149 ± 0.043	-0.203 ± 0.089	2.28	0.021	108	5.207 ± 0.039
25 to 34	80	5.699 ± 0.018	19	5.421 ± 0.077	-0.278 ± 0.091	1.06	0.003	99	5.645 ± 0.044
35 to 44	45	6.482 ± 0.085	9	6.100 ± 0.191	-0.382 ± 0.209	1.83	0.064	54	6.419 ± 0.079
45 to 54	15	7.142 ± 0.132	7	8.371 ± 0.131	+0.929 ± 0.151	2.06	0.040	22	7.567 ± 0.134
55 to 64	27	8.419 ± 0.358	3	8.000 ± 0.306	+0.181			30	8.437 ± 0.322
65 and over	16	10.256 ± 0.502	2	12.040 ± 0.219	+1.791			18	10.456 ± 0.465
	292		182					474	

TABLE 4—Age Changes in the Radial Velocity of Both Sexes (Mean Radial Velocity and Its Standard Error)

Age, Years	Males		Females		Difference and Its Standard Error	Difference		Both Sexes	
	Number	Mean	Number	Mean		Standard Error	Probability Integral	Number	Mean
5 to 9	17	7.176 ± 0.099	10	4.970 ± 0.099	-0.206 ± 0.140	1.17	0.142	27	5.100 ± 0.073
10 to 14	19	7.473 ± 0.058	12	5.08 ± 0.200	+0.073 ± 0.223	0.25	0.892	31	7.474 ± 0.097
15 to 19	22	6.045 ± 0.081	40	6.107 ± 0.048	+0.062 ± 0.106	0.53	0.532	62	6.092 ± 0.053
20 to 24	31	6.897 ± 0.070	82	6.261 ± 0.011	-0.336 ± 0.073	4.60	0.000	116	6.859 ± 0.039
25 to 34	93	6.990 ± 0.038	24	6.638 ± 0.075	-0.252 ± 0.081	3.47	0.000	117	6.870 ± 0.036
35 to 44	52	7.835 ± 0.053	11	7.188 ± 0.070	-0.199 ± 0.088	5.68	0.000	66	7.779 ± 0.051
45 to 54	63	8.621 ± 0.061	10	8.120 ± 0.190	-0.501 ± 0.200	2.53	0.012	73	8.555 ± 0.062
55 to 64	39	9.110 ± 0.151	3	8.600 ± 0.151	-0.510			42	9.074 ± 0.141
65 and over	16	9.675 ± 0.683	1	9.167 ± 0.107	-0.208			19	9.642 ± 0.573
	355		198					553	

TABLE 5—Age Changes in the Diastolic Blood Pressure of Both Sexes (Mean Diastolic Blood Pressure and Its Standard Error)

Age, Years	Males		Females		Difference and Its Standard Error	Difference		Both Sexes	
	Number	Mean	Number	Mean		Standard Error	Probability Integral	Number	Mean
5 to 9	16	63.438 ± 2.916	8	56.750 ± 1.585	-6.688 ± 3.433	1.23	0.219	24	61.208 ± 2.503
10 to 14	19	67.632 ± 2.651	12	64.167 ± 2.524	-1.465 ± 2.252	0.15	0.633	31	65.965 ± 1.571
15 to 19	23	68.087 ± 2.206	47	71.511 ± 1.309	+6.124 ± 2.642	2.43	0.016	70	72.400 ± 1.205
20 to 24	36	75.361 ± 1.213	82	71.885 ± 0.872	-0.776 ± 1.194	0.92	0.603	118	75.693 ± 0.729
25 to 34	99	76.696 ± 0.769	25	73.160 ± 0.504	-3.136 ± 1.683	2.01	0.041	124	75.903 ± 0.687
35 to 44	55	82.145 ± 1.002	14	77.929 ± 2.379	-1.216 ± 2.581	1.63	0.104	69	81.290 ± 0.947
45 to 54	67	87.582 ± 1.158	9	76.000 ± 4.120	-6.982 ± 4.561	1.44	0.150	76	82.803 ± 1.145
55 to 64	41	81.927 ± 1.708	3	84.333 ± 1.702	+2.406			44	82.091 ± 1.610
65 and over	21	82.762 ± 2.208	3	86.000 ± 1.000	+3.238			24	83.167 ± 1.941
	377		203					580	

On the whole, the dispersion of mean values for the velocity of the aortic pulse wave (table 6) is essentially constant for males and females up to about 40 years, when the dispersion of values as measured by their standard deviations is significantly increased. The increasing variation from the mean aortic velocity that occurs in the later decades of life can best be explained on the ground that with increasing age, especially after the fortieth year, there begin to appear, in spite of the most meticulous selection of cases, the various manifestations of degenerative diseases of the cardiovascular system which may alter the elasticity of the arterial wall to various degrees. In the age span from 5 to 40 years the ranges of biologic variation from the mean velocities are approximately constant. From then on, regressive changes in the blood vessels alter the picture.

This is in accordance with Aschoff's¹⁷ division of the life of arteries of the elastic type, especially of the aorta, into three periods: first, the ascending period, lasting until the age of 35, characterized by an equal increase of all tissue elements of the vessel wall; second, the summit between the ages of 35 to 45, without marked arterial changes; third, the descending stage, from the age of 45 on, characterized by various degenerative changes. Foster²⁸ showed also that elastic tissue of the aorta attains its maximum growth at the age of 35. Then regressive changes begin to occur. Arteriosclerotic changes in the aorta between the ages of 35 and 40 years are not uncommon.

When the differences between the standard deviation of the velocity of the radial pulse wave for successive age groups (table 7) are compared, particularly in males, the deviations appear to become significant at 50 years. At 55 years the difference is definitely significant. In the aorta, the difference of the standard deviations (table 6) becomes significant at 40 years of age. From this it can be concluded that the degenerative changes, at least in males, commence later in life in the medium-sized vessels than in the aorta. This corroborates the view that the wear and tear begins in the aorta.

The standard deviations for the velocities of both aortic and radial pulse waves (tables 6 and 7) in the old age period (graphically represented in charts 2 and 3) are obviously large. This may be due to the fact that the persons in this group were not true normal subjects. On the other hand, the large values indicate that there may occur in the older ages a variety of pathologic changes. The changes may so alter the condition of the aortic wall as to produce wide variations in elasticity reactions. For example, a hardening of the wall will increase the velocity of the pulse wave, whereas marked ectasia will tend to lower pulse wave velocity. Moreover, tortuosity tends to an error in measurement of

28 Foster, L. S. Changes Occurring in the Elastic Fibers of the Aorta with Advancing Age, *J. M. Research* **21**: 297, 1909.

TABLE 6—Differences Between the Standard Deviations of Aortic Velocity for Successive Age Groups

Age, Num Years, ber	Males				Females				Both Sexes					
	Standard Deviation and Its Standard Error	Difference and Its Standard Error	Diff S F	Proba- bility Integral	Num ber	Standard Deviation and Its Standard Error	Difference and Its Standard Error	Diff S F	Proba- bility Integral	Num ber	Standard Deviation and Its Standard Error	Difference and Its Standard Error	Diff S E	Proba- bility Integral
5-9	0.362 ± 0.074	-0.053 ± 0.092	0.78	0.562	11	0.492 ± 0.110	+0.033 ± 0.151	0.78	0.704	24	0.431 ± 0.064	+0.006 ± 0.084	0.07	0.944
10-14	0.309 ± 0.055	+0.077 ± 0.080	0.90	0.68	15	0.570 ± 0.104	-0.151 ± 0.114	1.32	0.187	32	0.437 ± 0.055	-0.016 ± 0.068	0.24	0.810
15-19	0.386 ± 0.066	+0.079 ± 0.096	0.45	0.657	39	0.799 ± 0.046	-0.024 ± 0.055	0.44	0.660	108	0.421 ± 0.040	-0.026 ± 0.048	0.05	0.960
20-24	0.425 ± 0.057	+0.004 ± 0.065	0.06	0.952	77	0.775 ± 0.080	-0.019 ± 0.062	0.79	0.430	99	0.395 ± 0.027	+0.040 ± 0.041	0.98	0.327
25-34	0.429 ± 0.031	+0.178 ± 0.069	2.00	0.016	19	0.326 ± 0.051	+0.511 ± 0.175	1.48	0.179	74	0.453 ± 0.081	+0.139 ± 0.064	2.17	0.030
35-44	0.567 ± 0.060	+0.310 ± 0.111	2.70	0.006	9	0.511 ± 0.175	+0.215 ± 0.115	1.32	0.129	72	0.574 ± 0.036	+0.384 ± 0.110	3.49	0.000
45-54	0.877 ± 0.093	+0.916 ± 0.270	3.70	0.001	7	1.075 ± 0.310	-0.023			70	0.973 ± 0.095	+0.778 ± 0.247	3.15	0.001
55-64	1.823 ± 0.273	+0.121 ± 0.476	0.28	0.779	3	0.472	-0.183			18	1.726 ± 0.228	+0.180 ± 0.400	0.45	0.673
65+	1.944 ± 0.375				2	0.249					1.916 ± 0.729			

TABLE 7—Differences Between the Standard Deviations of Radial Velocity for Successive Age Groups

Age, Num Years, ber	Males				Females				Both Sexes					
	Standard Deviation and Its Standard Error	Difference and Its Standard Error	Diff S F	Proba- bility Integral	Num ber	Standard Deviation and Its Standard Error	Difference and Its Standard Error	Diff S E	Proba- bility Integral	Num ber	Standard Deviation and Its Standard Error	Difference and Its Standard Error	Diff S E	Proba- bility Integral
5-9	0.397 ± 0.070	+0.020 ± 0.099	0.20	0.841	10	0.297 ± 0.070	+0.368 ± 0.158	2.33	0.018	27	0.373 ± 0.052	+0.157 ± 0.086	1.83	0.067
10-14	0.417 ± 0.070	-0.044 ± 0.091	0.48	0.631	12	0.665 ± 0.112	-0.240 ± 0.150	1.60	0.110	31	0.530 ± 0.068	-0.115 ± 0.078	1.47	0.141
15-19	0.373 ± 0.058	-0.023 ± 0.072	0.14	0.660	10	0.427 ± 0.048	-0.035 ± 0.057	0.61	0.742	62	0.415 ± 0.068	-0.001 ± 0.047	0.02	0.984
20-24	0.341 ± 0.042	+0.028 ± 0.050	0.56	0.575	82	0.790 ± 0.071	-0.028 ± 0.061	0.62	0.335	116	0.414 ± 0.027	-0.027 ± 0.037	0.73	0.466
25-34	0.369 ± 0.027	+0.013 ± 0.017	0.28	0.779	24	0.362 ± 0.051	-0.111 ± 0.072	1.51	0.124	117	0.387 ± 0.025	+0.028 ± 0.044	0.61	0.522
35-44	0.382 ± 0.038	+0.099 ± 0.037	1.74	0.082	11	0.251 ± 0.019	+0.318 ± 0.142	2.24	0.023	66	0.415 ± 0.036	+0.107 ± 0.037	1.88	0.060
45-54	0.481 ± 0.043	+0.447 ± 0.114	3.92	0.000	10	0.769 ± 0.131	+0.069			73	0.522 ± 0.044	+0.394 ± 0.110	3.88	0.000
55-64	0.928 ± 0.106	+1.719 ± 0.481	3.55	0.000	3	0.678	-0.186			42	0.916 ± 0.101	+1.515 ± 0.417	3.63	0.000
65+	2.647 ± 0.483				3	0.142				19	2.431 ± 0.405			

the distance traveled, and hence tends to lower the measured velocity of the pulse wave. It must also be kept in mind that persons age at varying rates after the age of 40 years, and a retardation in the rate of the aging processes leads to a lower velocity of the pulse wave. Persons whose arteries age faster have an increased velocity of the pulse wave. The wide spread of the central zone of variability (standard deviation) after the age of 40 may be due to all these factors affecting in variable degree the individual velocities of the pulse wave. For aortic velocity (table 6) the standard deviation for the age group from 45 to 54 years is 0.958. In the age group from 55 to 64 years,

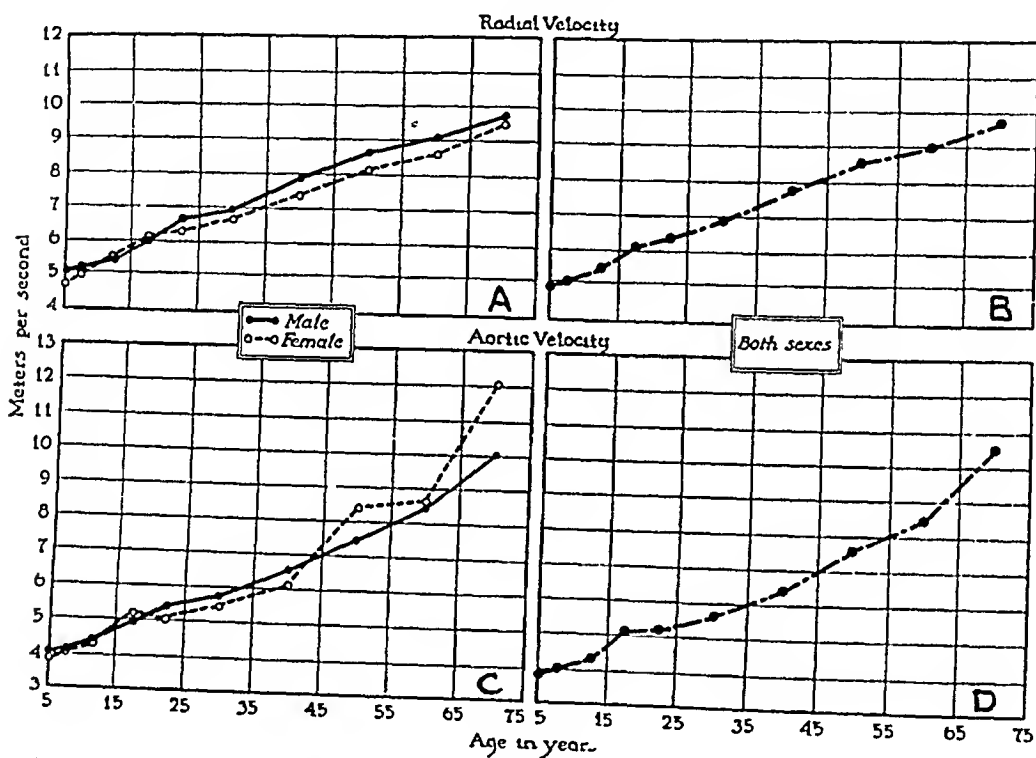


Fig 4—Graphs of the point to point curves, showing the progressive increase of the mean radial and aortic pulse wave velocities for males and females and for the combined sexes with age

the value jumps to 1.736. For radial velocity (table 7) the increase is delayed ten years. It appears, therefore, that the marked degenerative changes are established in the aorta before they appear in the radial vessels. Studies of the volume elasticity coefficient of isolated vessels undoubtedly would yield considerable information in this respect and would help to explain the increasing variability found in old age. The standard deviation and its standard error for both sexes between the period from 55 to 64 is 0.916 ± 0.104 , and for the age of 65 and over, 2.431 ± 0.405 . The latter variations have not been presented as sigma lines in figure 3. Instead, dotted lines have been extended from points on the graph corresponding to 60 years. In all probability, two thirds

of the cases for the ages above 60 would tend to fall within the boundaries of these dotted lines, provided more cases could be recorded. It is also probable that if it were possible to obtain records from older persons representing the higher strata of life, the velocities of their pulse waves would tend to fall within the designated zone.

It is interesting to compare the age difference and standard errors for both sexes. In males the mean velocities of the radial pulse wave as compared to the mean aortic velocities, remain consistently higher until the age of 65 years is reached. After 65, the mean aortic velocity passes the mean radial velocity (tables 3 and 4). As regards females, with the exception of those in the age period from 45 to 54 years, a similar situation obtains until the age period from 55 to 64. At this period, both mean radial and mean aortic velocities become the same, $86 \frac{\text{seconds}}{\text{meters}}$. After this age the mean velocity of the aortic pulse wave exceeds the mean radial velocity.

When one compares the velocities of the radial and aortic pulse waves in both sexes (tables 8 and 9) one finds that between the ages of 14 and 20, the radial and aortic velocities in females exceed these velocities in males. This phenomenon appears to be a common observation in growth curves of males and females. Scammon²⁹ showed from growth curves obtained in postnatal life that because females pass through most of the transition of the developmental period a little earlier than males the physiologic age of girls is usually greater than that of boys of the same chronological age. This difference probably accounts for the increased velocity in females in the age period from 14 to 20.

Table 3 shows that there are no significant sex differences in the aortic velocities from the age of 5 to 15 years. However, after 15 years significant sex differences appear. Thus for example, in the age period from 15 to 20 years, the difference between the two means is 3 times the standard error. Such a difference would occur by chance alone only one time in a hundred. In the age period from 35 to 44, the difference between the means is 1.83 times the standard error. This difference may be considered on the border-line of significance, for it would occur by chance alone only six times in a hundred. Likewise, in the age period between 45 and 54 the standard error of the difference may be considered possibly significant its difference being 2 times its standard error, and the probability of it occurring by chance alone less than five in a hundred. The sex differences in the mean velocity of radial pulse waves do not become significant until the 20 year age period (table 4). After 20 years, the differences are significant, i. e., this difference is consistently greater than 2.5 times the standard error mean.

²⁹ Scammon, R., in Morris, H. Human Anatomy, ed 8, Philadelphia, P. Blakiston's Son & Co, 1925.

TABLE 8—Differences Between the Mean Aortic Velocity for Successive Age Groups

Age, Num Years ber	Males				Females				Both Sexes			
	Difference and Its Standard Error		Diff S E	Probab- ility Integral	Difference and Its Standard Error		Diff S E	Probab- ility Integral	Difference and Its Standard Error		Diff S E	Probab- ility Integral
	Mean	Num ber			Mean	Num ber			Mean	Num ber		
5 9 13	4 131 ± 0 147	11	1 26	0 207	4 000 ± 0 156	15	1 46	0 144	4 071 ± 0 080	24	2 16	0 081
10 14 17	4 341 ± 0 077	15	4 40	0 000	4 313 ± 0 147	39	5 68	0 000	4 328 ± 0 078	32	8 14	0 000
15 19 18	4 878 ± 0 094	39	4 40	0 000	5 228 ± 0 065	77	0 63	0 329	5 118 ± 0 058	57	1 27	0 204
20 24 31	5 352 ± 0 078	77	3 88	0 000	5 149 ± 0 043	19	3 03	0 002	5 207 ± 0 039	108	7 42	0 000
25 34 80	5 699 ± 0 048	19	3 77	0 000	5 421 ± 0 077	9	3 30	0 001	5 645 ± 0 044	54	8 60	0 000
35 44 45	6 482 ± 0 085	9	7 99	0 000	6 100 ± 0 191	7	4 82	0 000	6 419 ± 0 079	52	7 26	0 000
45 54 45	7 442 ± 0 132	7	60 00	0 000	8 371 ± 0 431	3			7 367 ± 0 194	30	2 49	0 012
55 64 27	8 419 ± 0 358	3	2 76	0 010	8 600 ± 0 306	2			8 437 ± 0 322	18	3 57	0 000
65+ 16	10 256 ± 0 502	2	2 98	0 003	12 050 ± 0 249				10 456 ± 0 465			

TABLE 9—Differences Between the Mean Radial Velocity for Successive Age Groups

Age, Num Years ber	Males				Females				Both Sexes			
	Difference and Its Standard Error		Diff S E	Probab- ility Integral	Difference and Its Standard Error		Diff S E	Probab- ility Integral	Difference and Its Standard Error		Diff S E	Probab- ility Integral
	Mean	Num ber			Mean	Num ber			Mean	Num ber		
5 9 17	5 176 ± 0 069	10	1 99	0 047	4 970 ± 0 079	12	2 41	0 016	5 100 ± 0 073	27	3 09	0 002
10 14 19	5 453 ± 0 068	12	4 66	0 000	5 703 ± 0 200	40	2 82	0 005	5 474 ± 0 097	31	5 48	0 000
15 19 22	6 045 ± 0 081	40	5 52	0 000	6 103 ± 0 063	82	1 95	0 051	6 082 ± 0 053	62	4 20	0 000
20 24 34	6 597 ± 0 059	82	4 76	0 000	6 261 ± 0 043	24	4 38	0 000	6 359 ± 0 039	116	9 64	0 000
25 34 93	6 930 ± 0 038	24	14 69	0 000	6 638 ± 0 077	14	7 26	0 000	6 870 ± 0 036	117	14 66	0 000
35 44 52	7 885 ± 0 053	14	9 12	0 000	7 386 ± 0 070	10	3 62	0 000	7 779 ± 0 051	66	9 70	0 000
45 54 63	8 624 ± 0 061	10	2 98	0 007	8 120 ± 0 190	3			8 555 ± 0 062	73	3 33	0 001
55 64 79	9 110 ± 0 151	3	0 81	0 418	8 600 ± 0 451	3			9 074 ± 0 143	42	0 96	0 337
65+ 16	9 675 ± 0 083	3			9 467 ± 0 107				9 642 ± 0 573	19		

ing that the differences in the velocity of the pulse wave would not occur oftener than once in a hundred times on the basis of chance alone

When aortic velocities (table 8) for males between the age periods from 5 to 9 and from 10 to 14 are compared, the difference is only 1.26 times the standard error, indicating that the age change in young males is not significant. The difference in aortic velocity between the 5 to 9 and 10 to 14 year groups in females is likewise of no significance. However, the difference in the velocity of the radial pulse wave (table 9) for males between the corresponding age periods is probably significant, the difference being 1.99 times the standard error, indicating that the difference would occur through chance alone only four and a half times out of a hundred chances. For females the standard

TABLE 10—*Comparison of the Correlation of Diastolic Blood Pressure With Aortic and Radial Velocities for Both Sexes*

Age, years	Number	Aortic Velocity				Radial Velocity			
		$r \pm SE$	r^* SE	P†		$r \pm SE$	r^* SE	P†	
5-9	20	0.627 ± 0.224	2.80	0.005	24	0.146 ± 0.209	0.70	0.484	
10-14	32	0.312 ± 0.180	1.73	0.083	31	0.326 ± 0.183	1.78	0.073	
15-19	56	0.418 ± 0.135	3.10	0.002	61	0.224 ± 0.167	1.34	0.180	
20-24	107	0.071 ± 0.097	0.73	0.466	113	0.289 ± 0.094	3.07	0.002	
25-34	99	0.166 ± 0.101	1.64	0.101	116	0.047 ± 0.093	0.51	0.610	
35-44	53	0.231 ± 0.139	1.66	0.097	63	0.170 ± 0.127	1.41	0.159	
45-54	51	0.160 ± 0.141	1.13	0.258	73	-0.072 ± 0.118	0.61	0.542	
55-64	30	0.466 ± 0.186	2.51	0.012	42	0.211 ± 0.156	1.35	0.177	
65 & over	18	0.270 ± 0.243	1.11	0.267	19	0.085 ± 0.236	0.36	0.719	
All ages	466	0.533 ± 0.046	11.59	0.000	542	0.863 ± 0.043	20.07	0.000	

* r represents the correlation coefficient and SE its standard error

† P is the probability integral

error of the difference between the same age period is 2.41 and therefore significant, because this difference would occur through the operation of chance alone only one and a half times in a hundred chances.

When both sexes are combined, the difference between the velocity of the radial and the aortic pulse wave for successive age groups is significant throughout except in the period from 20 to 25 years for aortic velocity.

Table 5 shows the diastolic blood pressure progressively increasing with age for males and females. Diastolic pressure is consistently lower in females than in males of corresponding ages. Significant variations between males and females appear in the age group from 15 to 19 years, in which the difference is 2.34 times the standard error. In the age group between 25 and 35, the sex difference in diastolic pressure is 2.04 times the standard error and therefore significant.

In order to determine whether any quantitative relationship exists between the velocity of the pulse wave and diastolic pressure, correlation

coefficients were determined for radial velocity and diastolic pressure and for aortic velocity and diastolic pressure. Since the correlation technic is based on the assumption of a rectilinear relation between the two variables, the velocities were plotted against diastolic pressure by means of spot diagrams. Their trends appear to be approximately rectilinear, hence this technic is applicable to this material. Table 10 shows a comparison of the correlation of the diastolic pressure with the aortic and radial velocities of the combined sexes. The correlation coefficients for all ages combined were 0.533 ± 0.046 for aortic velocity and 0.864 ± 0.043 for radial velocity. However, such correlations are of questionable value in view of the age increase in velocities and diastolic blood pressure. The factor of age increase could account for the significant correlation found. This explanation is supported by the observation that the correlations for radial velocity and diastolic pressure for the 5 and 10 year age periods are much lower than the value of the correlation coefficient for all ages combined, and that only one of the six correlations for groups after growth is complete is significant. To prove the reliability of the significance of these correlations, it would be necessary to treat the data by partial correlation when age could be held constant. The same factor of growth may account for the sex difference in correlation found by Hafkesbrung and Ashman³⁰. Table 10 shows in the age period of from 20 to 24 a positive correlation for radial velocity. As mentioned before, of the hundred and thirteen persons in this group, approximately 80 per cent were females. We therefore probably have a slightly positive correlation in the radial velocity, particularly in the female group. Hafkesbrung and Ashman derived from approximately ninety-six observations the coefficients of correlation between subclavicular-radial and carotid-radial velocities with diastolic pressures. In both instances they found significant correlations in females, with correlation coefficients of 0.662 ± 0.056 and 0.529 ± 0.093 , respectively. Significant coefficient correlations were not found in males. However, if one considers that the age spread from which their correlation coefficients were computed varied from 17 to 36 years, it appears that the correlations of these investigators are spurious, as the age changes are probably responsible for the high correlation values. Similarly, the high correlation of coefficients found by Sands in her series of eight cases must be disqualified on similar ground. It seems, therefore, that the coefficient of correlations as computed in table 10 for radial velocities between 20 to 24 years of age represents a more accurate value.

In figure 4 the effect of age on the mean velocity of the pulse wave is again graphically represented in the form of point to point curves

30 Hafkesbrung, R., and Ashman, R. Pulse Wave Velocity in Ninety Subjects, *Am J Physiol* **100** 89, 1932

Figures *A* and *C* demonstrate again the increasing radial and aortic velocity in females in the age period between 12 and 20 as compared to that in males. The abrupt rise in aortic velocity at the age of 60 for both sexes may be accounted for by the fact that only a few observations were made on elderly females and that they all had high pulse wave velocities.

It is interesting to compare the mean radial velocities, from table 4, with those obtained by Bramwell, Hill and McSwiney²². Their series comprised seventy-four observations on both males and females varying in age from 4 to 84 years, and in pulse wave velocity from 4.7 to 8.6 meters per second. Fifty-three of their observations were made on persons below 25 years of age, while only twenty-one were made on older subjects. In this study, a total of five hundred and fifty-three observations was made on the velocities of the radial pulse wave alone.

It is obvious from table 11 that the figures on the velocity of the pulse wave are in excellent agreement, except after 45 years of age.

TABLE 11—*Comparison of the Mean Velocities of the Radial Pulse Wave*

Age periods	5-9	10-14	15-19	20-24	25-35	36-44	45-54	55-64
Bramwell, Hill and McSwiney ²²	5.3	5.7	6.0	6.3	6.7	7.3	7.6	8.0
Hallock	5.1	5.5	6.05	6.3	6.9	7.7	8.6	9.0

The mean velocities of Bramwell and his associates from 50 years upward are based on seven observations, while the mean values in my observations are based on approximately seventy-five.

Excluding the higher age group, the table shows the close agreement obtained by the use of two different recording instruments, in one instance, the hot wire sphygmograph used by Bramwell, Hill and McSwiney, and in the other, the segment capsule apparatus employed in this study.

CONCLUSIONS

The essential factors which modify arterial elasticity in man have been discussed and the literature reviewed. The fundamental theoretical considerations from which it is possible to evaluate arterial elasticity in living man from the velocity of the pulse wave have been briefly reviewed.

A method has been described by which the transmission time of the pulse wave through the aortic iliac vessels can be determined.

Within the limitations of these data, the following conclusions are drawn:

1. There is a progressive increase of the velocities of the aortic and radial pulse waves (arterial rigidity) with age, from a value of 4.1 meters per second in midchildhood to 5.2 meters per second at 22

years of age and to 10.5 meters per second at 65 years of age for aortic velocity, and in the brachial-radial vessels in midchildhood from a value of 5.1 meters per second to 6.3 meters per second at 22 years of age and to 9.6 meters per second at 65 years of age.

2 The velocity of the radial pulse wave in males is greater than that in females, except in the age period between 10 and 19 years. During this period, the velocity of the female pulse wave slightly exceeds that of the male. This is probably due to the fact that the physiologic age of females is greater than that of males during this period of life.

3 The velocity of the aortic pulse wave in males exceeds the velocity of the aortic pulse wave in females, except in the age period between 15 and 19 years. Here again the velocity of the pulse wave in females exceeds that in males for the same reason as was stated in the preceding paragraph. The velocity of the aortic pulse wave in females exceeds that in males after the age of 45. This discrepancy is probably due to the fact that less than ten observations were made on females for each ten year interval after the age of 35.

4 The velocity of the radial pulse wave is consistently higher than that of the aortic pulse wave until the 65 year age period is reached, indicating that the transmission time of the pulse wave is more rapid through the medium-sized vessels than through the larger arteries, such as the aorta and iliac vessels.

5 The dispersion of individual values for pulse wave velocities about the mean velocity of the aortic pulse wave as measured by the standard deviation is essentially the same from 5 to 40 years, after which it increases rapidly and significantly. The dispersion of individual values about the mean radial velocity is essentially the same from 5 to 50 years, after which it increases rapidly and significantly. Thus the increase in variability in radial velocity lags ten years behind that of the aortic velocity. These findings suggest that the greater dispersion of values for pulse wave velocity is caused by pathologic changes in the blood vessels, occurring earlier in the aorta. The effect of these changes is to increase the rigidity of the aortic-iliac tubing.

6 The differences between the mean velocity of the aortic pulse wave for successive age groups of the combined sexes are all significant, except for the age period between 20 and 25 years. When the sexes are considered separately, the mean difference between the 5 to 9 and the 10 to 14 year period is not significant in either sex. Likewise, the difference in the mean pulse wave velocity is not significant between the age groups of 15 to 19 and 20 to 24 in females.

7 When the differences between the mean velocities of the radial pulse wave for successive age groups for the combined sexes are considered, they are all significant except from the age of 65 and over. When the sexes are analyzed separately, the differences between the

15 to 19 and 20 to 24 year age groups for females are on the border-line of being significant. The differences in the mean velocity for successive ages are all significant in the male.

8 Sex differences as regards the velocity of the radial pulse wave do not become significant until the second decade is reached. However, when the aortic velocity is considered, sex changes become significant at 15 years of age. In the age period between 35 and 44 years, the age change is on the border-line of significance. There is no significant difference in mean diastolic pressure between males and females, except in the age periods from 15 to 19 and from 25 to 34.

9 The correlation found in this study and that found by other workers between the diastolic blood pressure and the velocities of the radial and aortic pulse waves cannot be considered valid until more extensive analyses are made with the age factor eliminated.

Dr. Edith Boyd, from the Institute of Child Welfare and Department of Anatomy, University of Minnesota, gave valuable assistance in the preparation of the statistical work in this paper.

LATENT ACUTE RHEUMATIC CARDITIS AS DETERMINED AT AUTOPSY

ITS OCCURRENCE

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In routine autopsies at the Presbyterian Hospital, it has been occasionally observed that a patient dying of a nonrheumatic condition, and often with a history of never having suffered from rheumatic infection, nevertheless showed lesions in the heart indicative of this disease. A search through the literature failed to disclose any description of a series of such cases, although there were a few scattered references to this coincidence. Geipel¹ recorded a case of contracted kidneys showing Aschoff bodies in the myocardium and an adherent pericardium. He also stated that Aschoff mentioned a case of Askanazy's in which scanty Aschoff bodies occurred although other signs of rheumatic infection were absent. Fraenkel² described three cases of verrucous endocarditis (in one of which the myocardium contained numerous Aschoff bodies) in which there was no history of rheumatic infection. Pappenheimer and Von Glahn³ recorded two cases that had no history of rheumatism in which Aschoff bodies were found in the myocardium. Swift⁴ mentioned two cases in which myocardial weakness was the only clinical feature, and in which the only distinct lesions revealed at autopsy were Aschoff bodies in the myocardium. Von Glahn and Wilshusen⁵ described two cases of syphilitic aortitis which had no history of rheumatic fever in which Aschoff bodies were found in the myocardium. Libman mentioned two similar cases, one occurring with typhoid fever.

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1 Geipel, P. Untersuchungen über rheumatische Myokarditis, *Deutsches Arch f klin Med* **85** 75, 1905

2 Fraenkel, E. Ueber Myocarditis Rheumatica, *Beitr z path Anat u z allg Path* **52** 597, 1912

3 Von Glahn, W. C., and Pappenheimer, A. M. Specific Lesions of Peripheral Blood Vessels in Rheumatism, *Am J Path* **2** 235, 1926

4 Swift, H. F. The Pathogenesis of Rheumatic Fever, *J Exper Med* **39** 497, 1924

5 Von Glahn, W. C., and Wilshusen, H. F. Syphilitic Aortitis and Acute Rheumatic Myocarditis, Report of Two Cases, *Proc New York Path Soc* **24** 71, 1924

and the other with peritonitis following perforation of a duodenal ulcer Rhoads,⁶ in a case of ulcerative endocarditis due to the meningococcus, found "a few areas which show necrotic bundles of collagen fibers surrounded by endothelial leukocytes, strongly suggesting Aschoff bodies" Clawson,⁷ in eight of fifty cases of syphilitic aortitis, found in the myocardium about the aortic ring "nodular proliferative areas comparable to Aschoff bodies"

It was decided to make a more detailed study of cases of lesions of rheumatic carditis that had no clinical history of this condition, to determine how frequently they occurred and what explanation could be offered. The autopsy records of the Presbyterian Hospital for the last five years were examined. In many cases the original sections were sufficient to demonstrate the rheumatic nature of the lesions in question, but when this was doubtful, additional blocks were cut from the preserved specimens (making a total of five or six blocks for each heart). The sections were stained with hematoxylin and eosin.

During the last five years ninety-six autopsies at this hospital were considered to show rheumatic lesions of the heart. In seventeen of these cases, death was due to some apparently unrelated cause and there was no recognizable clinical indication of an active rheumatic lesion. Cases of subacute bacterial endocarditis or frank mitral stenosis were not included in this consideration. These cases are divided into two groups: those showing Aschoff bodies in the myocardium, and those in which the evidence was derived mainly from the valvular lesions. Details concerning them are summarized in the accompanying table, and two illustrative cases are described.

REPORT OF CASES

CASE 1—History—A Filipino, aged 30, had gonorrhea in 1918. On Jan 6, 1929, he had pain in the lower dorsal part of the spine, and fever. His Wassermann reaction was 3 plus, and he received antisyphilitic treatment. His condition became worse and he was admitted to the hospital on April 6 with neoplasm of the left kidney. Tonsillitis developed. The heart was normal. Fever continued, and he died on May 16.

Autopsy—The left kidney was replaced by neoplasm (tubular adenocarcinoma). There were metastases in the left suprarenal gland, right kidney, liver, lungs, lymph nodes (abdominal and thoracic) and vertebrae. The heart weighed 260 Gm. The mitral leaflets were somewhat thickened with numerous small, yellowish vegetations near the margin. The aortic valves were slightly thickened.

Histologic Examination—The myocardium contained a number of Aschoff bodies. The endocardium of the right ventricle near the pulmonic valve was thickened with loose granulation tissue containing lymphocytes, plasma cells and Aschoff cells. The mitral valve was thickened by fibrous tissue containing masses

6 Rhoads, C. P. Vegetative Endocarditis Due to the Meningococcus, *Am J Path* 3: 623, 1927.

7 Clawson, B. J. Aschoff Nodule, *Arch Path* 8: 664 (Oct) 1929.

Cases Showing Lesions of Active Rheumatic Carditis Without Recognizable Clinical Symptoms

Autopsy Number	Age	Sex	Previous History of Rheumatic Fever	Clinical Condition of Heart	Autopsy Diagnosis	Evidence of Active Rheumatic Carditis
Cases Showing Aschoff Bodies in the Myocardium						
10,217	30	M	0	Normal	Tubular adenocarcinoma of kidney with metastases, Wassermann reaction +	Aschoff bodies in myocardium, endocarditis in right ventricle, thickening and vegetations of mitral leaflets
10,541	40	M		Normal	Chronic pulmonary tuberculosis, disseminated acute miliary tuberculosis	Aschoff bodies and scarring in myocardium, shortening and thickening of mitral leaflets with verrucae
10,543	34	F	0	Pericarditis (tuberculous)	Tuberculosis of tracheo bronchial lymph nodes, pericardium and fallopian tubes, disseminated acute miliary tuberculosis, Wassermann reaction +	Scanty Aschoff bodies in myocardium
10,648	35	M		Normal	Chronic pulmonary tuberculosis, disseminated acute miliary tuberculosis	Scanty Aschoff bodies in myocardium
11,005	37	F	0	Normal	Pulmonary tuberculosis, disseminated acute miliary tuberculosis	Numerous Aschoff bodies in myocardium, endocarditis in left ventricle
11,041	21	M	0	Normal	Acute otitis media with mastoiditis and suppurative lept meningitis (pneumococcus, type III)	Aschoff bodies in myocardium, mitral stenosis with verrucae
11,202	31	M	0	Normal	Chronic glomerular nephritis with edema and retinitis, tonsillitis (Staph aureus, Strep haemolyticus)	Aschoff bodies in myocardium, thickening of mitral leaflets with cellular infiltration and verrucae
11,228	28	M	3 years ago	Normal	Carcinoma of rectum with metastases, pelvic abscess, bacteremia (gram negative bacillus)	Scanty Aschoff bodies in myocardium, thickening and verrucae of mitral leaflets and aortic cusps
11,252	16	F			Abortion, acute endometritis and peritonitis	Scanty Aschoff bodies in myocardium
11,375	52	M	0	Normal	Carcinoma of esophagus, acute tracheitis, arteriosclerosis	Scanty Aschoff bodies in myocardium
Cases of Rheumatic Endocarditis in Which Aschoff Bodies Were Not Found						
10,234	36	F	0	Normal	Bilateral nephrolithiasis with hydronephrosis and suppurative pyelonephritis, pulmonary tuberculosis, arteriosclerosis, bacteremia (gram negative bacillus)	Active endocarditis of mitral leaflets with verrucae
10,257	33	M	0	Normal	Lobar pneumonia (pneumococcus type I)	Active endocarditis of mitral leaflets with verrucae
10,283	48	M	0	Normal	Ulcers of esophagus and duodenum, broncho pneumonia	Active endocarditis of mitral leaflets with verrucae
10,348	33	M	0	Normal	Bronchial asthma, rupture of pleura, bilateral pneumothorax	Active endocarditis of mitral leaflets with verrucae
10,933	42	F	0	Normal	Acute suppurative peritonitis (Strep hemolyticus) following cholecystotomy, acute suppurative pleurisy	Mitral valvulitis with verrucae, swollen collagen fibers and collections of large mononuclear cells in myocardium
11,067	63	M	0	Normal	Carcinoma of stomach, combined sclerosis of spinal cord, arteriosclerosis, acute prostatitis	Active endocarditis of mitral leaflets with verrucae
11,184	40	M	0	Normal	Carcinoma of cecum (excised), peritonitis, lobular pneumonia	Active endocarditis of mitral leaflets with verrucae

of small round cells and Aschoff cells, the vegetations consisted of fibrinoid material, invaded at the base by fibroblasts. No bacteria were seen in the vegetations.

CASE 2—History—A cholecystotomy was performed on a woman, aged 42, on Feb 28, 1932. She began to have a fever on March 28. Her heart seemed normal. Empyema was discovered and drained on April 3. The pus contained streptococci. She died on April 4.

Autopsy—There was acute suppurative pleurisy with atelectasis of the right lung. Acute suppurative peritonitis of the subphrenic region due to *Streptococcus haemolyticus* was found. There were bilateral hydrosalpinx and chocolate cysts on the ovaries. The heart weighed 320 Gm. The mitral valve showed nodular vegetations 0.5 mm across at the line of closure.

Histologic Examination—In the myocardium were a few swollen collagen fibers around the small arteries and a few large mononuclear cells. In some places the lesions closely resembled Aschoff bodies, but they were not quite typical. The nodules of the mitral valve consisted of structureless eosinophilic material, the neighboring portion of the valve was thickly infiltrated by large, irregular, elongated cells with basophilic cytoplasm and large vesicular nuclei. No bacteria were present.

COMMENT

From the table it is seen that there were ten patients with Aschoff bodies in the myocardium and seven patients with lesions of the mitral valve, histologically identical with rheumatic fever.

It is now generally agreed that the Aschoff body is a lesion specific for rheumatic fever (Swift,¹ Sacks,⁸ Coombs⁹ and many others). Clawson⁷ is the only recent worker who has attacked this conception. It is fair to assume that in at least ten of these cases an active rheumatic infection was present at the time of death, most probably this was also the case in the other seven. During the period under review there were 1,380 autopsies at this hospital, so that these seventeen cases represent approximately 1.2 per cent of the total series. Most of the patients were between the ages of 20 and 50, particularly between 30 and 40.

The association of active rheumatic lesions with the other conditions described may, or may not, be accidental. There is the theoretical possibility that other infections may activate a latent rheumatism. On the other hand the association may be purely fortuitous.

Analysis of the material offers little evidence for the possibility that certain other infections exert an activating influence. In the group of ten patients with rheumatic myocarditis, four died of military tuberculosis, five had acute nontuberculous infections of various kinds, three died of neoplasm, two gave a positive Wassermann reaction, but showed no anatomic evidence of syphilis, and one died of chronic nephritis.

8 Sacks, B. The Pathology of Rheumatic Fever, A Critical Review, *Am Heart J* 1:750, 1926.

9 Coombs, Carey F. Rheumatic Heart Disease, New York, William Wood & Company, 1924.

One patient was recorded as having hemolytic streptococci in the throat. In the group of seven patients showing only valvular lesions, one had pulmonary tuberculosis, six had acute nontuberculous infections, two died of neoplasm, and three had miscellaneous conditions, including nephrolithiasis, ulcers of the esophagus and duodenum and bronchial asthma.

It would seem that these conditions were too varied to have any logical relationship with the rheumatic lesions of the heart. A large number of the patients suffered from miscellaneous infections, especially lobular pneumonia, but many were terminal conditions that occurred with equal frequency in persons who showed no postmortem evidence of rheumatic fever. The only possible exception to this conclusion is presented by the occurrence of miliary tuberculosis in four of the ten patients with rheumatic myocarditis. A search through the records of 1,380 necropsies revealed forty-four cases of miliary tuberculosis (3.2 per cent), and of the ninety-six cases of rheumatic fever four were associated with miliary tuberculosis (4.2 per cent). Conversely, during this period the rheumatic cases comprised 7.7 per cent of the total number of autopsies, and of the forty-four patients with miliary tuberculosis four (9 per cent) showed rheumatic myocarditis. Consequently, it would seem that the combination of these two conditions does not occur more commonly than might be expected from the frequency of either condition separately. In any case, the number of combined cases is too small to furnish any reliable conclusion. In this connection it may be remembered that various investigators, especially Reitter and Lowenstein¹⁰ in recent years, claimed to have found tubercle bacilli in the blood of a large percentage of patients with rheumatic fever. But the technical methods employed by these workers were so destructively criticized by Wilson¹¹ that such evidence for a specific association must be regarded with caution.

The second possible explanation is that these patients died during the occurrence of a rheumatic carditis not sufficiently intense to give rise to clinical signs recognizable in the face of the symptoms of the main disease. It is well known that such a concealed carditis has taken place in persons in whom mitral stenosis developed without any clinical history of rheumatic fever. The proportion of the cases described to the total number of autopsies during this period (1.2 per cent) is not unduly high for a city in which rheumatic fever is as common as it is in New York.

10 Reitter, C., and Lowenstein, E. Ueber den pathogenetischen Zusammenhang des akuten Gelenksrheumatismus mit der Tuberkelbazillämie, *Wien klin Wchnschr* 45 293, 1932.

11 Wilson, G. S. Tuberculous Bacillaemia, Medical Research Council, Spec Rep Ser 182, 1933.

SUMMARY

A series of cases is described in which evidence of rheumatic myocarditis or endocarditis was discovered at autopsy, although the presence of an active rheumatic infection had not been recognizable during life. No correlation could be established between the rheumatic disease and any one of the various pathologic conditions found. It is therefore concluded that the association is accidental. It appears that in addition to those whose condition is diagnosed clinically as rheumatic fever, 12 per cent of the other patients dying at the Presbyterian Hospital also have active rheumatic disease.

EFFECTS OF VACCINES AND BACTERIAL AND PARASITIC INFECTIONS ON EOSINOPHILIA IN TRICHINOUS ANIMALS

WESLEY W SPINK, M D

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Little is known concerning the function of the eosinophil white blood cell. Its origin and life cycle are still a matter of controversy. In man, the eosinophil normally constitutes from 1 to 4 per cent of the circulating leukocytes, and an increase is of diagnostic value in several diseases. However, it is well known that normal guinea-pigs may have as many as 30 per cent eosinophils. Brown¹ first recognized the diagnostic importance of eosinophilia in trichinosis. He recognized, however, that in severe infections the circulating eosinophils may be either absent or few.

Opie² produced in normal guinea-pigs with marked eosinophilia, infections with *Bacillus tuberculosis*, *Bacillus pyocyaneus*, *Bacillus mucosus-capsulatus* and *Streptococcus pyogenes*. During the course of the infection, the eosinophils disappeared not only from the blood but from the tissues. Coincident with their disappearance from the blood, there was an accumulation of eosinophils near the site of inoculation. Canon³ observed a diminution of eosinophils in septic processes. Zappert⁴ found the number of these cells reduced in pneumonia, typhoid fever and erysipelas. Similar clinical findings were reported by Turk,⁵ Staubli⁶ and Nageli.⁷

Since eosinophilia is of diagnostic value in trichinosis, the question arises whether secondary infections may reduce the number of these cells to such an extent as to make the diagnosis uncertain. The studies reported in this paper were undertaken to determine (1) the number

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1 Brown, T. R. *Bull. Johns Hopkins Hosp.* **8**, 79, 1897.

2 Opie, E. L. *Am. J. M. Sc.* **127**, 988, 1904.

3 Canon, P. *Deutsche med. Wchnschr.* **18**, 206, 1892.

4 Zappert, J. *Ztschr. f. klin. Med.* **23**, 227, 1893.

5 Turk, W. *Klinische Untersuchungen über das Verhalten des Blutes bei acuten Infektionskrankheiten*, Vienna, W. Braumüller, 1898.

6 Staubli, C. *Trichinosis*, Wiesbaden, J. F. Bergmann, 1909.

7 Nageli, O. *Blutkrankheiten und Blutdiagnostik*, Berlin, W. de Gruyter & Company, 1919.

of eosinophil cells in the circulating blood and organs of trichinous guinea-pigs inoculated with bacteria, other parasites and vaccines, and (2) the relation of the number of eosinophils to the modes of encystment of *Trichinella*

METHODS

Guinea-pigs obtained from one source and approximately 3 months old were used throughout this study. These animals are readily infected with *Trichinella spiralis*, after which their blood picture becomes similar to that of trichinosis in man, with the exception of the peculiar and little understood inclusions (Kurloff bodies) in the cytoplasm of some of the mononuclear cells.

An increase in the circulating eosinophils was induced by feeding *Trichinella spiralis* by two methods. In earlier experiments, guinea-pigs were starved for twenty-four hours and then forcibly fed with heavily infected, trichinous guinea-pig meat. It was sometimes difficult to find encysted larvae in the muscles of guinea-pigs infected in this manner. A more effective method used in later studies was to give an enormous number of freed living larvae by means of a pipet inserted into the esophagus. The larvae were freed from infected meat by the method described by Augustine and Theiler⁸

Stained paraffin sections of muscles (masseter and diaphragm), lungs, liver, spleen, bone marrow and lymph nodes were made from animals killed during the course of the experiments. The number and appearance of the eosinophils were carefully noted in all the sections, and the muscles were examined for encysted parasites to determine any variation from their normal histologic aspect. The sections were stained with eosin-methylene blue, but as an aid in the studies of the muscles, the following stains were also employed: Mallory's phosphotungstic acid hematoxylin, Mallory's aniline blue stain and the latter with acid fuchsin omitted.

The following micro-organisms and vaccines were employed: the Saranac H-37 strain of tubercle bacilli, a fresh culture of *Staphylococcus aureus*, a strain of *Trypanosoma equiperdum* maintained in guinea-pigs and a triple vaccine containing typhoid and paratyphoid A and B bacilli.

As a basis for later study and comparison, the pathologic process of the muscle invaded by *Trichinella* is briefly described. The immediate effect on the muscle fiber in which the larvae has established itself is more or less degeneration. Within the muscle fiber the worm grows rapidly, it becomes coiled and then encysted. In the latter process, a capsule consisting of collagen fibrils laid down by the stimulated connective tissue gradually thickens and contracts into a hyaline layer, and then may become calcified. In the early stages of encystment, at each pole of the cyst there is an infiltration of leukocytes, including eosinophils. Through the entire muscle there is a diffuse cellular infiltration, and occasional eosinophils are found. There is evidence of muscular regeneration.

EXPERIMENTAL WORK

EXPERIMENT 1—*Tubercle Bacilli*—(A) A subcutaneous injection of 0.0005 Gm of the H-37 culture of tubercle bacilli suspended in sterile saline solution was made into the right inguinal region of four guinea-pigs. Fifteen days later, trichinous meat was fed to three of these animals and to one normal guinea-pig. The remaining animal served as a tuberculous control. Charts 1 and 2 show the

⁸ Augustine, D. L., and Theiler, H. *Parasitology* 24: 60, 1932

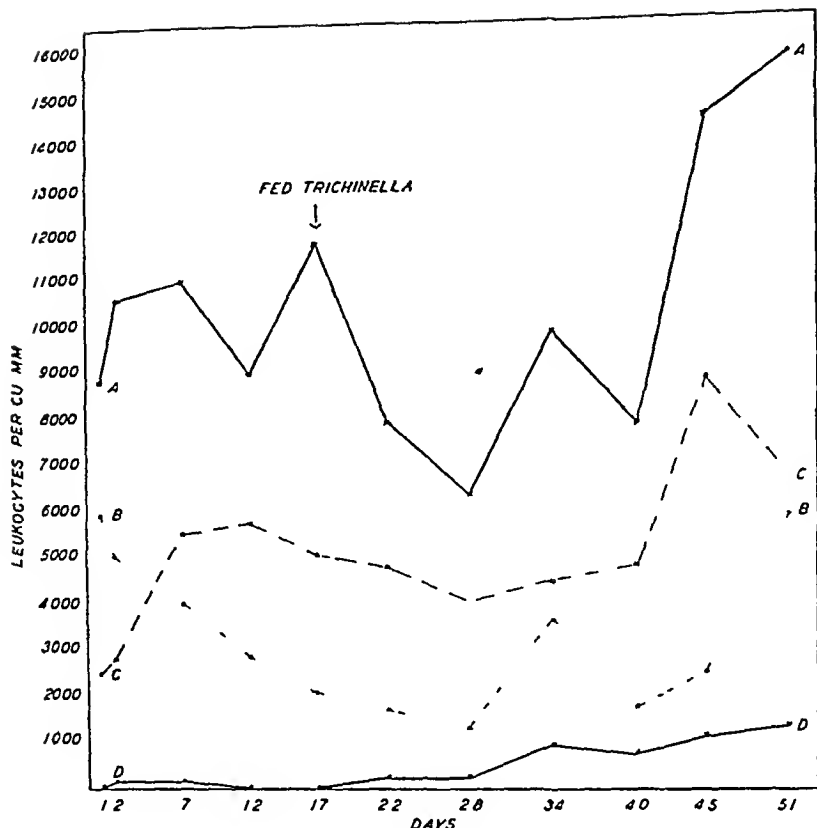


Chart 1—The course of the white blood cells in an animal infected with *Trichinella spiralis* A, curve for the total white blood cell count, B, curve for the polymorphonuclear neutrophil leukocytes, C, curve for the lymphocytes, D, curve for the eosinophil leukocytes

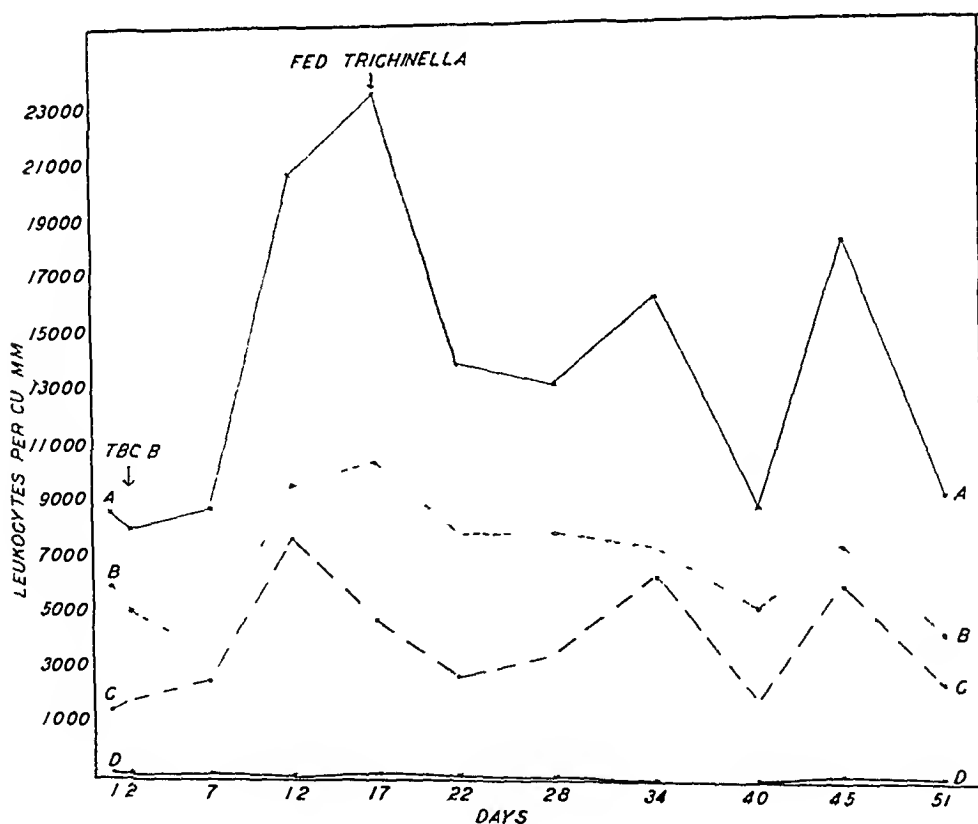


Chart 2—The course of the white blood cells in an animal infected with B tuberculosis and subsequently with *Trichinella spiralis* A, curve for the total white blood cell count, B, curve for the polymorphonuclear neutrophil leukocytes, C, curve for the lymphocytes, D, curve for the eosinophil leukocytes

course of the leukocytes in the trichinous animal and in one of the tuberculous-trichinous guinea-pigs. These charts show the typical results obtained in the other animals of this experiment.

In the normal trichinous pigs in this and succeeding experiments there developed an absolute increase of eosinophils, a slight decrease in polymorphonuclear leukocytes and an absolute increase in lymphocytes. In the tuberculous-trichinous pigs, there were few or no eosinophils (not more than 15 per cent) and the polymorphonuclear-lymphocyte ratio was in favor of the former cell, with a slight increase in the lymphocyte level as the infections progressed. There were inconstant changes in the monocytes, and the total leukocyte curve in all the animals in this experiment was variable.

The postmortem examination of animals with trichinosis alone showed an active bone marrow with many eosinophil myelocytes and leukocytes. There were large numbers of eosinophil leukocytes in the spleen and lungs, and in the cellular infiltration around the encysted parasites in the muscle. The bone marrow of the tuberculous-trichinous animals contained about the same number of eosinophil cells, but there were fewer eosinophil myelocytes and an increase of the mature type.

(B) In the preceding experiment, the animals were infected with tubercle bacilli before being fed with trichinous meat. For comparison, four guinea-pigs were fed with trichinous meat, and after the establishment of an eosinophilia they were inoculated with the same quantity of the H-37 strain as that used in experiment (A).

Chart 3 records the course taken by the white blood cells in one of the animals, which is characteristic of that in the other three. On the twentieth day after the feeding of trichinous meat, the eosinophils were 8 per cent. Tuberculosis was then superimposed on trichinosis, and the cells declined to 0.5 per cent during a period of seventeen days. There was an absolute increase in the polymorphonuclear leukocytes, with at first a decrease and later an increase in the lymphocytes. The total leukocyte count was not constant.

Postmortem examination revealed no differences in appearance of either muscle or parasites in the tuberculous-trichinous guinea-pigs as compared with trichinous guinea-pigs. However, the bone marrow, spleen and lungs of the former group had fewer eosinophils. There were none in the lymph nodes examined. The essential difference between the results of this experiment and the preceding one is that animals in which the tubercle bacillus was injected before trichinosis developed showed more eosinophils in the bone marrow, spleen and lungs than when the procedure was reversed.

EXPERIMENT 2—*Killed Tubercle Bacilli*—The preceding experiments were repeated, using killed instead of living tubercle bacilli. The material injected consisted of a suspension of 0.001 Gm. of the culture sterilized in an autoclave, in 1 cc. of saline solution.

The killed tubercle bacilli caused no decrease in the number of eosinophils, no appreciable changes in the total leukocyte counts and no variation in the histologic appearance of stained sections whether the injections were made before or after the establishment of trichinosis in guinea-pigs.

EXPERIMENT 3—*Staphylococcus Aureus*—(A) Trichinous meat was fed to four guinea-pigs to induce an eosinophilia. On the twenty-first day, when the eosinophil cells had risen to a high level, a fresh culture of *Staph. aureus* suspended in saline solution was injected into the subcutaneous abdominal tissue of

three of the animals. The fourth animal was left as a trichinous control, while a fifth served as an uninfected control. Within twenty-four hours, there were redness and swelling at the site of the injection, with marked reduction in the number of circulating eosinophils. Two days later, there appeared an area of necrosis about 2 cm in diameter, and the number of eosinophils continued to decline. Five days after the injection the lesions were healing, and the number of eosinophils had increased. At this time, a second inoculation of the organisms was made adjacent to the initial lesion. The tissue response was the same as in the first instance, and again the eosinophil level was reduced. As the lesions healed, the eosinophil count rose, and in two or three weeks it reached the level

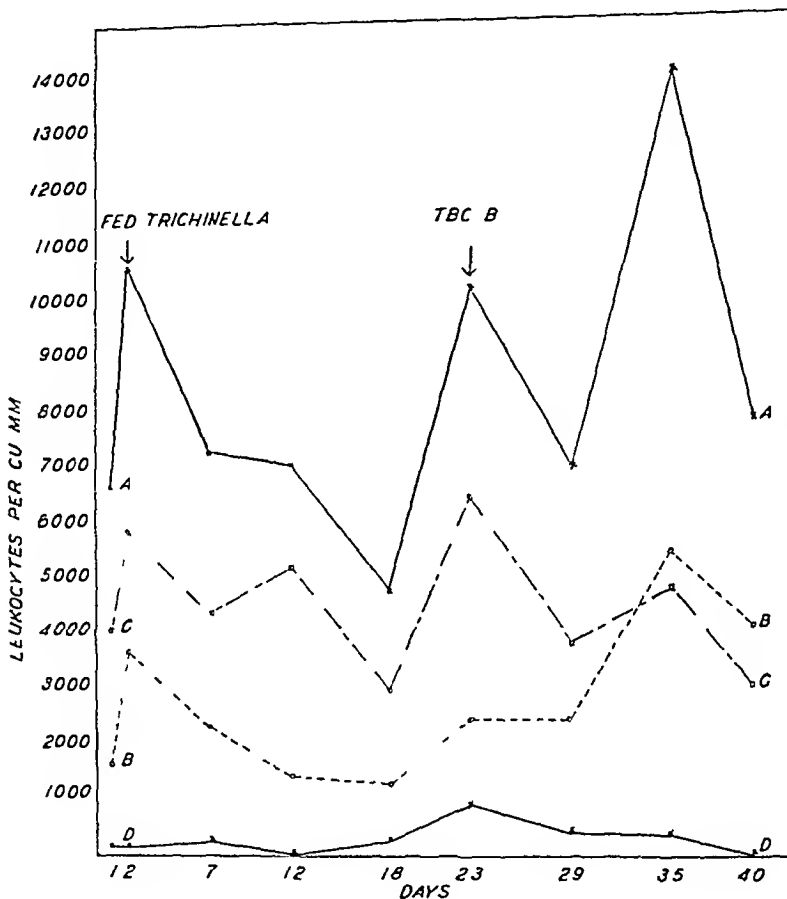


Chart 3—The course of the white blood cells in an animal infected with *Trichinella spiralis* and subsequently with *B tuberculosis*. *A*, curve for the total white blood cell count, *B*, curve for polymorphonuclear neutrophil leukocytes, *C*, curve for lymphocytes, *D*, curve for eosinophil leukocytes.

existing before the first injection of the staphylococci. Chart 4 illustrates the course of the white blood cells in one of the three animals which was typical of the group.

A normal animal, free from any known infection, was given two similar injections of *Staph aureus*. After the first injection, there was a slight leukopenia, with a decrease in polymorphonuclear leukocytes and an increase in lymphocytes. After the second injection, however, there was definite leukocytosis, with a rise in the polymorphonuclear leukocytes and a decrease in lymphocytes.

(B) Effect of Heat Certain of the animals used in this experiment were later employed to determine the effect on the eosinophil level following a rise in body temperature. The animals used included two of the guinea-pigs which had staphylococcal infections superimposed on trichinosis, the one with staphylococcal infection alone, and, as a control, another with no known infection. The animals were put into one cage and an electric heater was placed so that heat rays were directed on them. A thermometer hanging from the middle of the cage registered from 34 to 60 C for twenty hours the period of observation. Rectal temperatures and total and differential leukocyte counts were made just before heating, and four hours and twenty hours later. The rise in temperature in the animals varied from 1.5 to 3 C. Chart 4 records the effect of heat on the course

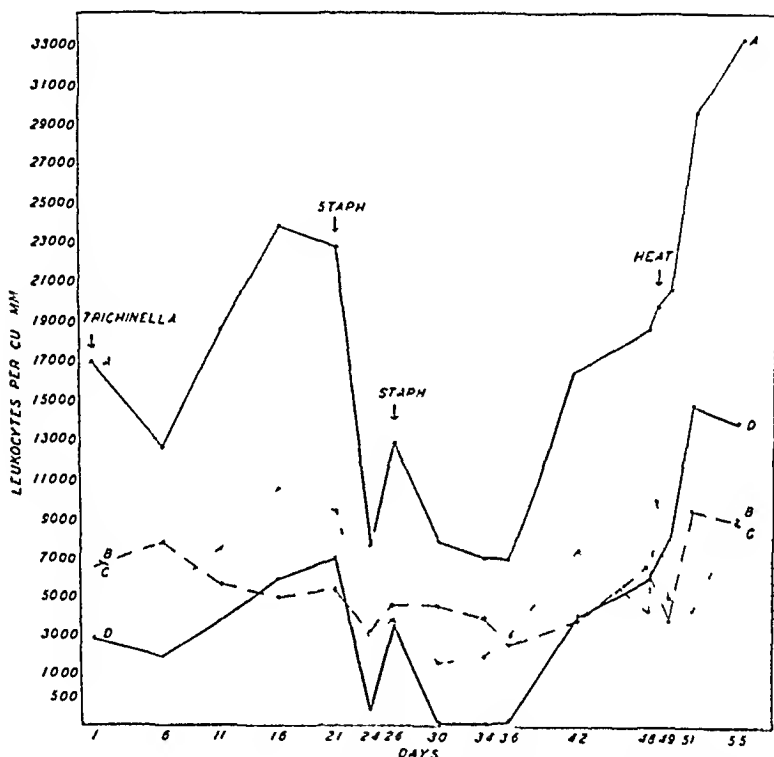


Chart 4—The course of the white blood cells in a trichinosis animal inoculated with *Staph aureus*, and on the forty-eighth day of the trichinosis infection subjected to a high degree of heat. A, curve for the total white blood cell count, B, curve for the polymorphonuclear neutrophil leukocytes, C, curve for the lymphocytes, D, curve for the eosinophil leukocytes

of the leukocytes in one animal, in addition to its previous reaction to *Staphylococcus*. In four hours there was an increase in the eosinophils and a rise in the polymorphonuclear leukocytes. Observations at the end of forty-eight hours showed marked leukocytosis and a rise in the eosinophils. It is of interest that the animals with the combined trichinosis-staphylococcal infection responded to the heat with an increase in the polymorphonuclear leukocytes and eosinophils, whereas the normal guinea-pig responded with a lymphocytosis. In the guinea-pig with the staphylococcal infection only, there was a rise in the polymorphonuclear leukocytes.

Perhaps of some importance are the changes in the blood in one of the guinea-pigs which were given *Staph aureus*. During the course of the trichinous infection (twenty-one days), the eosinophils failed to rise above 1 per cent. Shortly after the pyogenic infection was established, a peritonitis set in, and while the animal was in a moribund condition, large numbers of eosinophil cells made their appearance in the circulation and increased until death.

The histopathologic process in the organs of the trichinous animals was essentially the same as in the animals infected with both *Trichinella* and *Staphylococcus*. An animal which had had a trichinous infection and two staphylococcic abscesses and then been subjected to a high degree of heat (chart 4) showed one significant feature. In several sections of skeletal muscle, a septum of fibrous tissue between the muscle fibers was packed with eosinophils. This connective tissue was newly formed, as many mitotic fibroblasts were seen. The eosinophils were bilobular and elongated, as though all were moving in one direction. Nearby vessels in the tissue were dilated and showed perivascular cellular infiltration. The uninfected control which did not receive *Trichinella*, *Staphylococcus* or heat treatment possessed a high eosinophil count throughout the experiment. Sections of one of the lymph nodes presented the picture of mature eosinophil cells streaming along through the connective tissue septums. There was otherwise no evidence of an inflammatory process present in the tissue.

EXPERIMENT 4—Typhoid Vaccine—A stock preparation from the Massachusetts Antitoxin and Vaccine Laboratory containing 2,500,000,000 bacilli in 1 cc of killed typhoid and paratyphoid A and B bacilli was used in this experiment to determine the effect of a foreign protein reaction on the blood picture and the larvae.

Little information is available in the literature as to the effects of typhoid vaccine on guinea-pigs. The same dose as used for man was used at first 1 cc, 0.5 cc the first week and 1 cc the second and third weeks. Trichinous guinea-pig meat was fed to four animals, and simultaneously the first injection of vaccine was given in the subcutaneous abdominal tissue of each guinea-pig. The initial dose of 0.5 cc produced no change in the leukocyte counts, nor did the animals suffer any obvious ill effects. The dose was tripled, and 1.5 cc was injected one week later. Two of the four animals had a leukocytosis in the first twenty-four hours, and three showed a rise of the polymorphonuclear leukocytes, with a decrease of the lymphocytes and eosinophils. At the end of forty-eight hours, the eosinophils began to rise slowly, and the relationship between the polymorphonuclear cells and lymphocytes approximated that existing before injection. One week after the second injection, 3 cc was injected into the animals with approximately the same results.

Larger quantities of vaccine were given to another animal at different intervals. Trichinous guinea-pig meat was fed, and ten days later an initial injection of 2 cc was made. It is at this time in trichinosis that larvae are being carried in the blood stream to the muscles. Within twenty-four hours following the injection, there was a leukocytosis with a rise in the polymorphonuclear leukocytes and a decrease in lymphocytes, and the number of eosinophils dropped from 9 to 0.5 per cent. Five days after the first injection, 4 cc of vaccine was given, resulting in a leukocytosis, but there was no change in the polymorphonuclear-lymphocyte ratio, which had returned to normal forty-eight hours after the first injection. The eosinophil level remained the same as after the first injection. After six days, or on the twenty-first day of the trichinous infection, a third injection of 4 cc was made. The total white cell count showed a marked eleva-

tion of the polymorphonuclear neutrophil leukocytes and a decrease in lymphocytes. The eosinophils, which were 4 per cent before this injection, declined to zero in twenty-four hours, but rose to 7 per cent in four days, when a final dose of 4 cc was given with the same results, except that the eosinophils did not decline.

Normal animals which were given three injections of vaccine at intervals of a week, the dosage being 0.5 cc, 1.5 cc and 3 cc, respectively, showed a rise of the eosinophil level only following the third injection.

Microscopic examination of sections revealed only a light infestation of the muscles with *Trichinella*, making it impossible to arrive at any definite conclu-

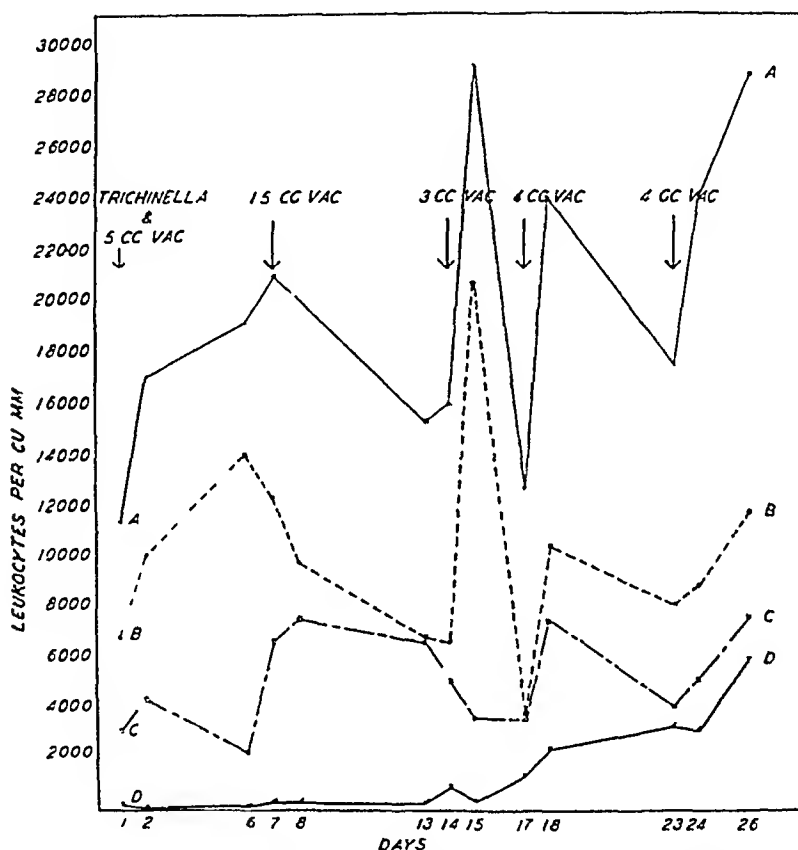


Chart 5—The course of the white blood cells in a trichinosis animal inoculated with typhoid vaccine. A, curve for the total white blood cell count, B, curve for the polymorphonuclear neutrophil leukocytes, C, curve for the lymphocytes, D, curve for the eosinophil leukocytes.

sions as to the effect of the vaccine. For this reason the studies were repeated on another group of animals.

To insure a heavy infection enormous numbers of freed living larvae were fed to four animals by means of a pipet. On the same day an initial injection of 0.5 cc of vaccine was administered. Subsequent injections of 1.5 cc, 3 cc, 4 cc and 4 cc were given after intervals of six, seven, three and six days, respectively. Chart 5 illustrates the course of the leukocyte counts in one of the animals typical of the group. It may be noted that there is a slight leukocytosis following each injection of typhoid vaccine, with a temporary diminution in the

eosinophils followed by an increase. There was an immediate rise in the polymorphonuclear leukocytes after each injection, while the lymphocytes tended to maintain a constant level throughout.

It is of interest that the trichinous controls lost weight, whereas all but one of the animals receiving typhoid vaccine gained in weight. Also, during the height of the disease (twentieth day) the trichinous controls were very irritable, and cried out when pressure was applied to the muscles. Those treated with vaccine showed no distress on being handled. D. L. Augustine⁹ recently carried out a number of experiments to determine the therapeutic value of typhoid vaccine in trichinous guinea-pigs. His results would seem to indicate that the vaccine had no effect on the course of the infection.

The muscles of all the animals in the last group were found to be heavily infected. The muscles of the normal trichinous animals and those which were given small doses of vaccine showed more muscular degeneration, cellular infiltration and edema than those which had large doses of vaccine, as shown in chart 5. There was no difference noted in the appearance or number of eosinophils in the organs of trichinous animals which had vaccine and those which did not. It is realized that this is too small a series from which to draw any definite conclusions.

EXPERIMENT 5—*Trypanosoma Equiperdum*—Citrated blood containing living *Trypanosoma equiperdum* was injected intraperitoneally into four animals, and later a trichinous infection was produced by feeding them freed living larvae. In another group of four animals, the procedure was reversed, with the trichinosis preceding the trypanosomiasis. Trypanosomes alone were given to two animals which served as controls.

In the controls, given trypanosomes alone, the total leukocyte count decreased during the first five days after infection, and then showed an elevation, but it did not return to the initial level. There was a decline in the polymorphonuclear neutrophils and eosinophils, while the lymphocytes consisting mostly of young forms increased.

Animals which were first infected with *Trypanosoma* and then fed *Trichinella* failed to show any rise in eosinophils. At first there was a leukopenia, but following the feeding of *Trichinella* there was a slight rise in the total white blood count. Trichinous guinea-pigs with an eosinophilia showed after the injection of trypanosomes a decline in the eosinophil cells and a leukopenia, but no essential change in the neutrophilic polymorphonuclear-lymphocyte ratio.

One control died as a result of a ruptured spleen. All the organs were markedly blanched. The bone marrow showed many mitotic figures, but only rare eosinophils. No eosinophils were found in the spleen or liver, but many were present in the alveolar capillaries and bronchi of the lungs.

The muscles of all the animals with the combined trypanosomiasis and trichinosis were heavily infested with *Trichinella*. There was a tendency toward less muscular destruction, cellular infiltration and edema than in the animals infected with *Trichinella* only. The bone marrow, spleen, liver and muscles showed the same appearance and number of eosinophil cells as in normal trichinous controls, but there were fewer eosinophils in the lungs.

⁹ Augustine, D. L. Personal communication to the author.

COMMENT

These observations confirm the experimental work of Opie² and Josey and Lawrence,¹⁰ and the clinical observations of other physicians, that acute infections cause a diminution in the number of the eosinophilic leukocytes in the peripheral blood. Previous investigations were made on normal guinea-pigs. In this study, an induced eosinophilia with a parasitic infection (*Trichinella spiralis*) responded similarly to secondary infection. Josey and Lawrence¹⁰ reported that both living and killed *Bacillus coli* injected into normal guinea-pigs caused a reduction in eosinophils. In this study, it was found that when virulent tubercle bacilli were injected into guinea-pigs the result was a diminution of the number of eosinophils, but that killed tubercle bacilli ten times the dose of the virulent organisms exerted no influence on the eosinophil level in normal and parasite-infested animals. With repeated injections of typhoid vaccine, there was not a reduction in the eosinophils, but the percentage steadily increased. This is probably due to the fact that the animals were sensitized to the protein injected. Biggart¹¹ observed a similar response with repeated injections of protein solutions containing peptone, egg albumin, casein and horse serum.

A histologic examination of the tissues of trichinous animals, and those with trichinosis plus a secondary infection, revealed eosinophil cells included in the cellular infiltration around the parasites in the muscle fibers. However, this observation was not constant. This may have led Opie¹² to state that in this respect trichinosis of guinea-pigs differs from that of the human subject, as he was unable to find eosinophil cells around degenerate muscle fibers at any stage in the disease.

Animals with tuberculosis or trypanosomiasis superimposed on a trichinous infection had not only a diminution in the number of eosinophil cells in the peripheral blood, but also less evidence of muscular destruction, edema of the muscle fibers and cellular infiltration around the encysted parasites than animals with trichinosis alone. An explanation of the foregoing observation may possibly be based on immunologic principles. The cellular infiltration, edema of muscle fibers and degeneration illustrate the animal's resistance to the invading parasites. I have observed with Augustine that if trichinous animals are given a second infection with *Trichinella spiralis*, the cellular infiltration around the young parasites is increased considerably. Many of the larvae are outside the muscle fibers and appear to be undergoing destruction due to the attacking leukocytes. Owing to the first infection, the animals have developed an immunity to the invading parasite, and encystment is more difficult in a second infection. Observations in this

10 Josey, A. I., and Lawrence, J. S. *Folia haemat* **48** 323, 1932

11 Biggart, J. H. *J. Path. & Bact* **35** 799, 1932

12 Opie, E. L. *Am. J. M. Sc* **127** 217, 1904

study of tissue reaction may be further evidence that an immunity to *Trichinella spiralis* is developed following the primary invasion of the larvae. Ducas¹³ and later McCoy¹⁴ showed that in rats infected a second time with *Trichinella spiralis* fewer worms developed in the intestinal tract. In the trichinous animals with tuberculosis or trypanosomiasis, there was lessened reaction in the muscles owing to the fact that the animal's powers of resistance were devoted not only to resisting the invading larvae, but probably, primarily, to the more virulent and commonly fatal infections.

I am unable to explain satisfactorily the lessened cellular infiltration, edema and muscular destruction in trichinous animals receiving large doses of typhoid vaccine. A general reaction to the vaccine is indicated by the fact that each injection was followed by a leukocytosis. These animals gained in weight and were less irritable than normal trichinous controls during the height of the disease.

Further study of the tissues of all the animals revealed accumulations of eosinophil cells. They were found in abundance in the lungs of the normal controls, the trichinous animals and those with trichinosis and a secondary infection. They were seen in the capillaries, within the alveoli, especially grouped around and in the walls of the smaller bronchi and in partially destroyed cells in the lumens. This was also observed by Opie¹². In a study of tissues from various parts of the body, this was the only evidence of destruction of these cells. Is it possible that after they have served their purpose they are excreted through the respiratory tract? Or, more pertinent, are they serving some purpose in being excreted there? It is well known that in patients with asthma, eosinophil cells are often found with ease in the sputum. I studied by ordinary methods the urine and stools of two patients with trichinosis having an eosinophilia of more than 50 per cent, and failed to find any evidence of excretion of the cells through these channels. However, Healy and his associates¹⁵ recently observed eosinophils in the stools of a patient with gastro-intestinal allergy.

In many of the animals, an accumulation of large numbers of eosinophil cells was found in connective tissue, especially in the lymph nodes, spleen, muscles and peribronchial tissue. Opie¹² and Kanthack and Hardy¹⁶ reported similar observations. Sometimes this connective tissue was newly formed, as mitotic figures were present. Similar observations led some of the earlier workers to believe that the eosinophil cell had its origin in connective tissue cells. Before the function

13 Ducas, R. L. *L'immunité dans la trichinose*, Paris, Jouve & Cie, 1921.

14 McCoy, O. R. *Am J Hyg* **14** 484, 1931.

15 Healy, James C., Gallison, Davis T., and Brudno, James. *New England J Med* **210** 123, 1934.

16 Kanthack, A. A., and Hardy, W. B. *J Physiol* **17** 81, 1894.

of the eosinophil is fully understood, this relationship will have to be explained

It is often stated that in certain diseases, for example scarlet fever and tuberculosis, eosinophil cells are present in the blood, mostly in the afebrile stages. In subjecting trichinous guinea-pigs to a high degree of heat so that their body temperatures were raised, the number of eosinophils, instead of being diminished, was elevated. Realizing that the number of animals studied is too small for definite conclusions, it would appear that it is not the temperature per se which causes a reduction of these cells, but rather something associated with the cause of the rise in temperature.

Throughout all the experiments, the animals were weighed periodically to see if there was a relationship between the number of circulating eosinophil leukocytes and the body weight. Opie¹² concluded that there is a direct relationship in the guinea-pig, and stated that an increase in weight is accompanied by a fall in the proportion of eosinophils, while a decrease in weight is accompanied by an increase in the number of the cells. In analyzing the weights and leukocyte counts of fifty animals, I could find no constant relationship.

While conducting this study, Dr. K. J. Thompson called my attention to a patient in the Fourth Medical Service of the Boston City Hospital, who had trichinosis complicated by a pyogenic infection. The summary of the case is as follows:

REPORT OF A CASE

A. P., a youth, aged 19, single, entered the hospital complaining of diarrhea of one week's duration and pains in the left leg. He had had intermittent chills and fever for one day, with no diarrhea. His temperature on entry was 103 F., and his pulse rate, 110. Essential positive findings on physical examination included a slightly enlarged and tender spleen, small maculopapular red blotches consistent with "rose spots," over the abdomen, open and infected ulcers of one week's duration on both feet, and soreness on palpation in the left popliteal region. A provisional diagnosis was made of typhoid fever. There was a slight leukocytosis, and no eosinophils were found in the blood. The pyogenic lesions on the feet were treated immediately on entry, and in four days were definitely improved. At this time the eosinophils were 6 per cent, and a diagnosis was made of trichinosis, which was verified by positive skin and precipitin tests. Later a biopsy of muscle revealed *Trichinella*.

What mechanism is involved in the diminution of the circulating eosinophil leukocytes in trichinous animals which are given a secondary infection? An endeavor was made to answer this by a study of the bone marrow. Evidence appears to favor the opinion that all eosinophil leukocytes have their origin in the bone marrow. In the preceding experiments, no evidence was found that with the decline of eosinophil cells in the peripheral blood there was as marked a reduction in the marrow. In the secondarily infected animals there were fewer eosinophil

myelocytes and evidence of a lessened production, but the total number of eosinophil cells was approximately the same as in trichinous animals without complications. It appears, then, that eosinophil cells are always present in the bone marrow, ready for entrance into the peripheral blood under certain influences. In the case of trichinosis, these cells enter the blood stream at a time when the larvae invade the muscles. Whether this is due to toxins liberated by the larvae at this stage or to the absorption of destroyed muscle is difficult to state, but whatever the mechanism, it is probably related to protein metabolism. If a trichinous animal is given a secondary infection, as with staphylococci, there is more of an immediate need for another type of leukocyte. But as soon as the acute stage of the pyogenic infection has passed, the eosinophil leukocyte again enters into the circulation. Previous observations on the reactions in the muscles and these hematopoietic responses indicate how appropriately these mechanisms of the body respond to various types of invasion.

SUMMARY

1 The number of circulating eosinophil leukocytes in animals infected with *Trichinella spiralis* was reduced following infection with B tuberculosis, *Staph aureus* and *Trypanosoma equiperdum*. Animals which had received repeated injections of typhoid vaccine responded with a rise in the eosinophil level. No change was noted following the injection of heat-killed tubercle bacilli.

2 Studies of the bone marrows from the same animals did not reveal a corresponding decrease in the number of eosinophil cells.

3 Trichinous animals having a superimposed infection of tuberculosis or trypanosomiasis had less reaction around the encysted parasites in the muscle than the control animals. Trichinous animals inoculated with typhoid vaccine showed similar changes in the muscles.

4 Trichinous animals subjected to a high level of dry heat responded with an absolute rise in the circulating eosinophilic leukocytes.

5 No relationship was found between the weights of animals and the level of eosinophilic leukocytes in the peripheral blood.

6 The number of circulating eosinophil cells did not appear to be related to the mode of encystment of *Trichinella spiralis* in the muscle.

ORAL AND DUODENAL ADMINISTRATION OF SINGLE LARGE DOSES OF PURE THYROXINE

COMPARISON OF CALORIGENIC EFFECTS WITH THOSE OF MONOSODIUM
THYROXINE AND THYROXINE IN ALKALINE SOLUTION

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CHICAGO

We have shown that single large doses of thyroxine in alkaline solution have about 63 per cent as much effect when administered by mouth as when given intravenously¹ However, the oral administration of the monosodium salt in tablet form produces only about 25 per cent as much effect as the intravenous administration of thyroxine in alkaline solution, when the comparison is made on the basis of the daily doses of the two substances required for maintenance of the basal metabolism of patients with myxedema at the normal level² As a continuation of our study of the calorogenic action of various forms of thyroxine we have now determined the effects of administering single large doses of pure thyroxine both by mouth and directly into the duodenum, and have compared them with the effects of oral administration of single large doses of monosodium thyroxine in tablet form and of thyroxine in alkaline solution

From the Department of Medicine, Rush Medical College, and the Presbyterian and Cook County hospitals

1 (a) Thompson, W O , Thompson, P K , Dickie, L F N , and Alper, J M Effect of Alkali on the Absorption of Thyroxine from the Gastro-Intestinal Tract, *Arch Int Med* **52** 809 (Nov) 1933 (b) Thompson, W O , Thompson, P K , Taylor, S G , III, Alper, J M , and Dickie, L F N The Effect of Various Compounds of Thyroxine on the Basal Metabolism, *Endocrinology* **18** 228, 1934

2 (a) Thompson, W O , Thompson, P K , and Dickie, L F N Monosodium Thyroxine, Desiccated Thyroid and an Impure Sodium Salt of Thyroxine Comparison of Their Effects When Administered Orally with the Effect of Thyroxine in Alkaline Solution Injected Intravenously, *Arch Int Med* **52** 576 (Oct) 1933 (b) Thompson, W O , McLellan, L L , Thompson, P K , and Dickie, L F N The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man The Relation Between the Iodine in Desiccated Thyroid and in Thyroxine, *J Clin Investigation* **12** 235, 1933

METHOD

As in the previous parts of this study we used only patients with definite myxedema, because of their greater response to all kinds of thyroid preparations. Five patients were used³. In the first patient the myxedema was spontaneous in the others it followed a subtotal thyroidectomy for exophthalmic goiter. The fourth patient also suffered from a mild postoperative tetany which caused practically no symptoms throughout the period of observation, during which time her serum calcium was about 8 mg per hundred cubic centimeters. The data on the third patient are not satisfactory because of irregular breathing, and his metabolic levels can only be approximated. The Sanborn-Benedict, Sanborn-Grafic and Benedict-Roth machines were used in making the determinations of the basal metabolic rate, and Aub-DuBois standards were used in the calculations. In computing the number of calories (excess calories) produced by a given dose of thyroxine, we have used a method described in previous communications⁴. Since the number of calories produced in excess of the basal rate is probably greater at higher than at lower levels of metabolism and since the method used takes into account only the basal calories, the actual excess calories recorded must be regarded as approximations and only of comparative and not absolute value. As the modes of administration of the various substances may be of importance, we have given them in detail in the legends.

All thyroxine used was crystalline synthetic thyroxine except the monosodium salt, which was in the form of tablets, each of which contained 1.03 mg of the salt. Kendall⁵ said that when thyroxine is dissolved in an excess of sodium hydroxide the disodium salt is formed. The monosodium salt is only slightly soluble in distilled water, whereas the disodium salt is said to be soluble to the extent of 4 per cent⁵. In all patients on whom data are reported here and elsewhere the alkaline solution of thyroxine (presumably the disodium salt) was prepared for oral administration by treating synthetic thyroxine with a weak solution of sodium hydroxide, except in the case of the first of two administrations of this substance to the second patient, when it was prepared by treating tablets of the monosodium salt in the same way.

For duodenal administration of thyroxine the position of the Rehfuess tube was always checked by fluoroscopy, the typical curve of the tube as it passed from the stomach into the duodenum leaving no doubt about its position. In addition, in the first patient a small amount of barium sulphate was injected through the tube the night preceding the administration of thyroxine and again about four and one-half hours preceding it. At the time of administration practically all the barium seemed to be in the ascending and transverse colons. In

3 All the data on the first patient and about two thirds of the data on the second patient were collected at the Cook County Hospital, and the remainder at the Rush Medical College and Presbyterian Hospital. Dr. Frederick Tice and Dr. Karl A. Meyer permitted us to collect data on the patients in the Cook County Hospital.

4 Thompson, W. O., Thompson, P. K., Brailey, A. G., and Cohen, A. C. The Calorigenic Action of Thyroxin at Different Levels of Basal Metabolism in Myxedema, *J. Clin. Investigation* 7: 437, 1929. Thompson, Thompson, Dickie and Alper¹⁰.

5 Kendall, E. C. Thyroxine, New York, The Chemical Catalog Company, Inc., 1929.

the third patient a small amount of barium sulphate was injected through the tube twenty minutes before the administration of thyroxine

The data are recorded in charts 1 to 6 and are summarized in table 1. It may be noted that in patients 1, 4 and 5 the oral adminis-

DATA

TABLE 1—*Comparison of Effects of Administering Thyroxine in Various Forms by Mouth and Duodenum to Five Patients with Myxedema*

Patient	Medication	Total Iodine Content of Substance Used, Mg	Basal Metabolic Rate Before Medication, per Cent Normal	Level to Which Basal Metabolic Rate Rose, per Cent Normal	Change in Basal Metabolic Rate, Points	Length of Time Basal Metabolic Rate Was Affected, Days	Number of Squares in Graph	Number of Excess Calories Produced
1	40 mg pure synthetic thyroxine suspended in distilled water, by duodenum	26.0	-39	-10	-1			
	100 mg pure synthetic thyroxine suspended in distilled water, by mouth	65.0	-40	-35	5	7		
2	10 mg synthetic thyroxine in the form of its monosodium salt (tablets), by mouth	6.5	-27	-22	15	50	426	6,485
	10 mg synthetic thyroxine in the form of its monosodium salt (tablets) treated with an alkaline solution	6.5	-11	-17	17	52	580	8,910
	50 mg pure synthetic thyroxine suspended in distilled water, by duodenum	32.5	-32	-29	3	15	31	485
	10 mg pure synthetic thyroxine in alkaline solution by mouth	6.5	-1	-10	24	62	8.7	13,025
3	10 mg pure synthetic thyroxine suspended in distilled water, by duodenum	6.5	-18	-14	4			
	10 mg synthetic thyroxine in the form of its monosodium salt (tablets), by mouth	6.5	-17	-11	6	24		
4	30 mg pure synthetic thyroxine suspended in distilled water, by mouth	19.5	-20	-18	2	6	9	130
	30 mg synthetic thyroxine in the form of its monosodium salt (tablets), by mouth	19.5	-22	-12	10	26	165	2,395
	10 mg pure synthetic thyroxine in alkaline solution, by mouth	6.5	-22	-7	15			
5	40 mg pure synthetic thyroxine suspended in distilled water, by mouth	26.0	-28	-24	4			
	40 mg synthetic thyroxine in the form of its monosodium salt (tablets), by mouth	26.0	-28	-20	8			

tiation of 100, 30 and 40 mg respectively, of pure thyroxine did not produce a clearcut change in the basal metabolic rate. There is some question of a change in the first patient following the administration of 100 mg. In this instance the basal metabolic rate rose from minus 40 to minus 35 per cent, and was back at its prethyroxine level in seven days. However, this change was too slight to be considered definite.

It should perhaps be regarded more seriously because subsequently the prolonged daily oral administration of large doses of pure thyroxine to the same patient raised the basal metabolic rate to normal, as will be reported later

It may also be noted that in the first three patients, single doses of 40, 50 and 10 mg, respectively, of pure thyroxine, when administered directly into the duodenum, were likewise without a definite effect on the basal metabolic rate

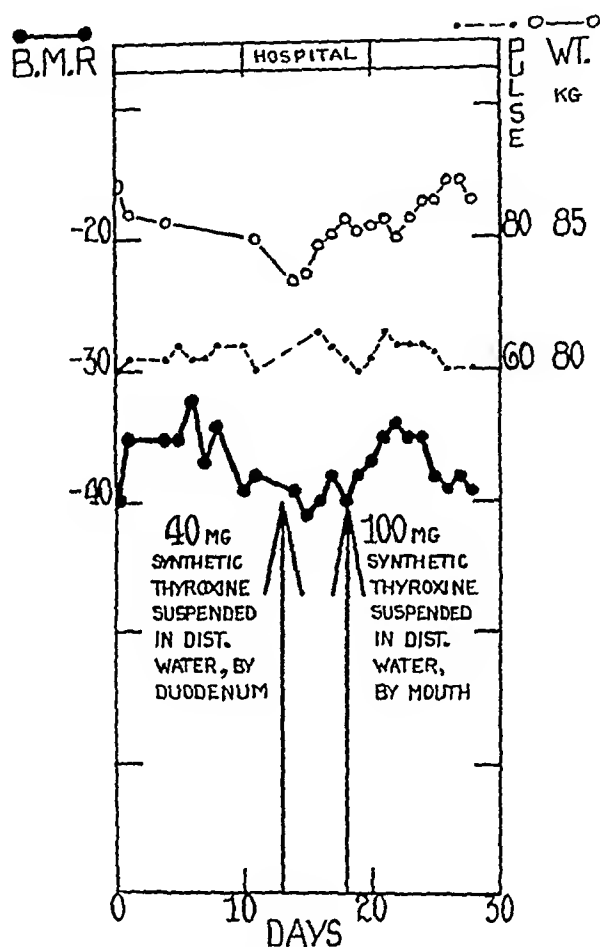


Chart 1 (Mrs P S, height, 166 cm, age 44) —The duodenal administration of 40 mg of pure synthetic thyroxine was made at 3 p m on Feb 9, 1933, through a Rehfuß tube which was in the duodenum about 10 cm. The thyroxine was administered in a suspension of lukewarm distilled water, a total of 375 cc being used, largely for rinsing. The patient had had lunch three hours before the administration. The oral administration of 100 mg of pure synthetic thyroxine was made at 7 50 p m on Feb 14, 1933, in a suspension of lukewarm distilled water, a total of 500 cc being used, largely for rinsing. The patient had received her usual three meals during the day, the evening meal having been served about 5 p m.

To the second, third, fourth and fifth patients, single doses of 10, 10, 30, and 40 mg, respectively, of thyroxine were administered by

mouth in the form of the monosodium salt. A definite, though slight, increase in the basal metabolic rate and some clinical improvement were noted in all. One of the first things apparent was that the effect in the second patient was greater than in the other three. Thus, in her, 103 mg of the monosodium salt raised the basal metabolic rate from minus 37 to minus 22 per cent, and resulted in the production of

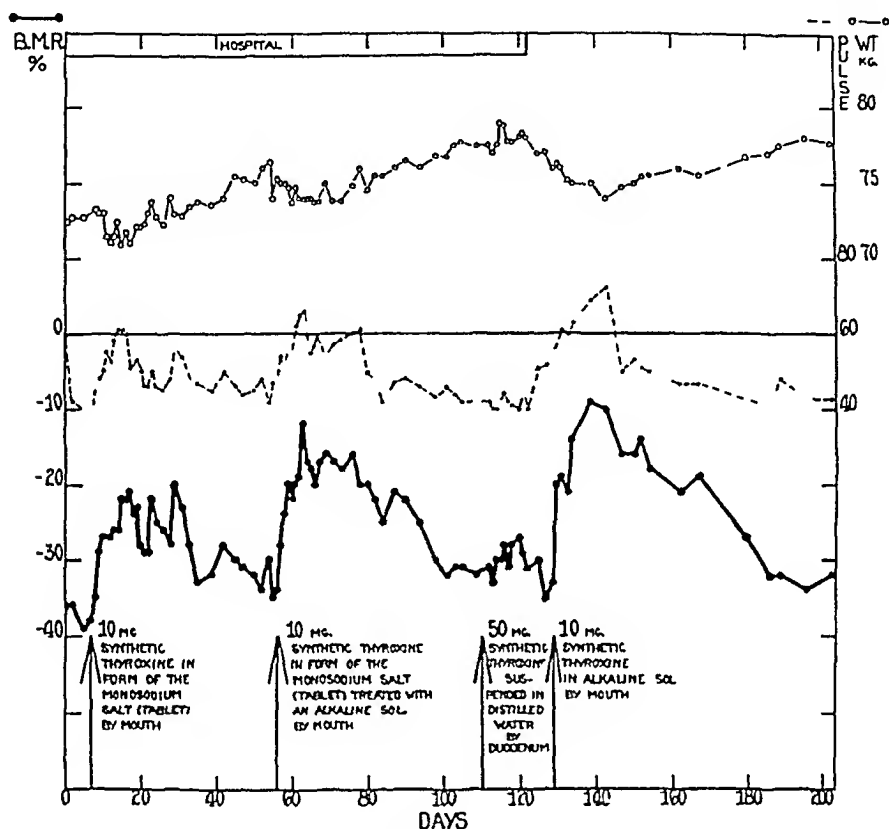


Chart 2 (Mrs B G, height, 158 cm, age 38)—The oral administration of 10 mg of thyroxine in the form of its monosodium salt was made at 6 p m on Nov 11, 1932, about 100 cc of distilled water being used to wash down the tablets. The patient had had her usual three meals during the day, supper having been served at 5 p m. The oral administration of 10 mg of thyroxine in the form of its monosodium salt, which had been treated with an alkaline solution, was made at 4 20 p m on Dec 30, 1932, a total of 5 drops of a 10 per cent solution of sodium hydroxide being used for solution and rinsing. In addition, 15 grains (0.96 Gm) of sodium bicarbonate was given in solution at 4 15 p m and 10 grains (0.64 Gm) in solution at 4 25 p m. A total of 200 cc of distilled water was used for all purposes. The patient had had breakfast, and had lunch at 12 noon. The duodenal administration of 50 mg of pure synthetic thyroxine was made through a Rehfuß tube at 4 30 p m on Feb 22, 1933, suspended in distilled water, a total of 400 cc of water being used, largely for rinsing. The patient had not eaten since the preceding night. The oral administration of 10 mg of synthetic thyroxine in alkaline solution was made at 1 20 p m on March 13, 1933, a total of 4 drops of 10 per cent solution of sodium hydroxide and 250 cc of distilled water being used for solution and rinsing. The patient had received no food since 5 30 p m the preceding day.

6,485 excess calories, whereas in the third patient, the same dose caused an increase of only from minus 17 to minus 11 per cent, in the fourth patient 30 mg caused an increase only from minus 22 to minus 12 per cent and the production of 2,395 excess calories, and in the fifth patient 40 mg caused an increase of only from minus 28 to minus 20 per cent. The reason for this variation in effect is not clear.

To the second and fourth patients we administered 10 mg of thyroxine by mouth in alkaline solution. As pointed out, it was

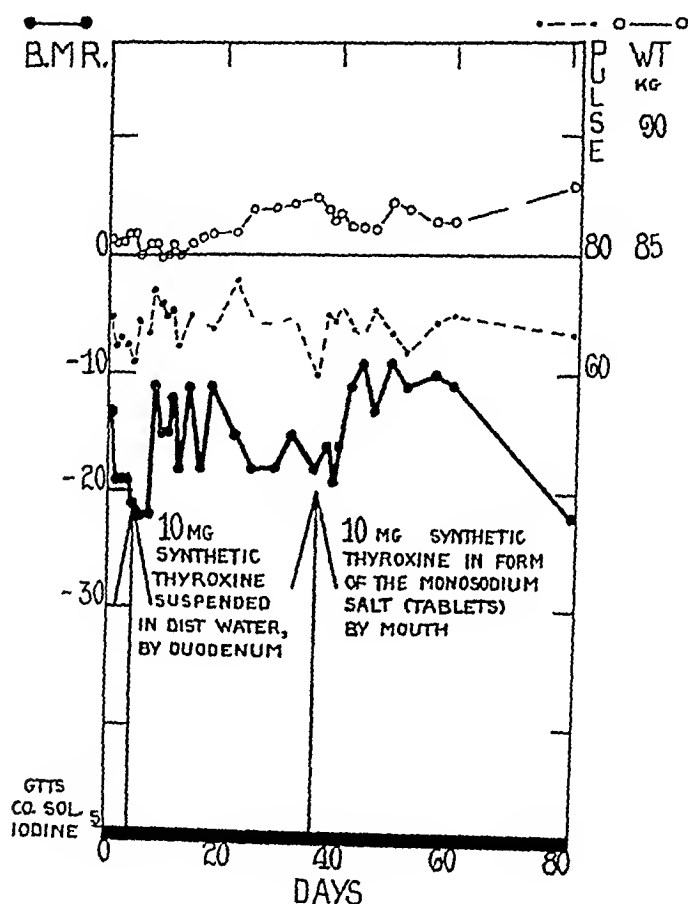


Chart 3 (Mr A H, height, 181 cm, age 47) —The duodenal administration of 10 mg of pure synthetic thyroxine was made at 6 50 p m on Jan 20, 1933, through a Rehfuß tube, in a suspension of distilled water, a total of 450 cc of water being used, largely for rinsing. The patient had not eaten since 8 p m of the preceding day, except for an Ewald meal six hours before the administration, most of which was aspirated, but he ate dinner twenty minutes after the administration. The oral administration of 10 mg of thyroxine in the form of its monosodium salt (10.3 mg of the salt) was made at 1 p m on Feb 21, 1933, in the form of tablets which were washed down with 450 cc of distilled water. The patient had had no breakfast or lunch.

administered twice in this form to the second patient. The first time the alkaline solution was prepared by treating tablets of the monosodium salt with sodium hydroxide and the second time by dissolving pure

crystalline thyroxine in an excess of sodium hydroxide. For some reason not clear at present, when the tablets were used the effect was less than when crystalline thyroxine was dissolved in an excess of sodium hydroxide. When the tablets were treated with sodium hydroxide some powder remained undissolved, which it was thought represented the base used in making the tablets (66 per cent sugar of milk and 33 per cent arrowroot starch) because the monosodium salt is soluble in a weak solution of sodium hydroxide. It is possible, however, that some of the monosodium salt was undissolved. When the tablets were used, a single dose containing the equivalent of 10 mg

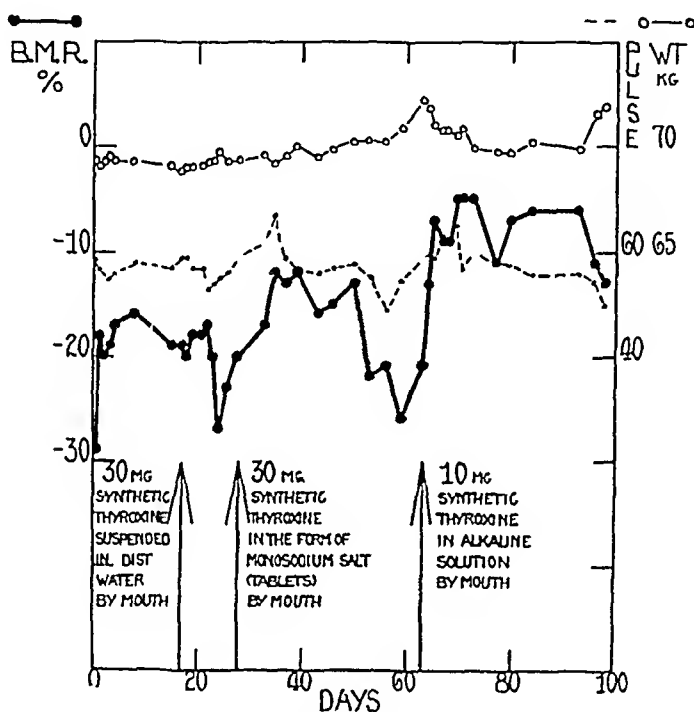


Chart 4 (Mrs C B, height, 152 cm, age 33) —The dose of 30 mg of pure synthetic thyroxine was given by mouth at 1 50 p m on Jan 26, 1933, the patient having fasted since the night before. It was given suspended in lukewarm distilled water, a total of 400 cc being used, largely for rinsing. The dose of 30 mg of thyroxine in the form of its monosodium salt (30.9 mg of the salt) was given by mouth in tablet form at 12 30 p m on Feb 6, 1933, the patient having had no food after 6 p m on February 5. The tablets were washed down with 400 cc of lukewarm distilled water. The oral administration of 10 mg of pure synthetic thyroxine in alkaline solution was made at 1 10 p m on March 13, 1933, using 4 drops of 10 per cent solution of sodium hydroxide and a total of 250 cc of distilled water for solution and rinsing. The patient had been fasting since the preceding night.

of thyroxine increased the basal metabolic rate from minus 34 to minus 17 per cent and caused 8910 excess calories to be produced. When the same dose of pure crystalline thyroxine was used after

dissolving it in an excess of sodium hydroxide, the basal metabolic rate was increased from minus 34 to minus 10 per cent and 13,025 excess calories were produced. In the fourth patient the administration of 10 mg of thyroxine in alkaline solution caused an increase in basal metabolic rate from minus 22 to minus 7 per cent. Thus, in the fourth patient, 10 mg of thyroxine in alkaline solution produced one and a half times as much effect as 30 mg in the form of the monosodium salt, and about twice as much effect as 40 mg in the form of the monosodium salt in the fifth patient.

Data reported here and elsewhere showing the effects of administering single large doses of thyroxine in various forms and by various

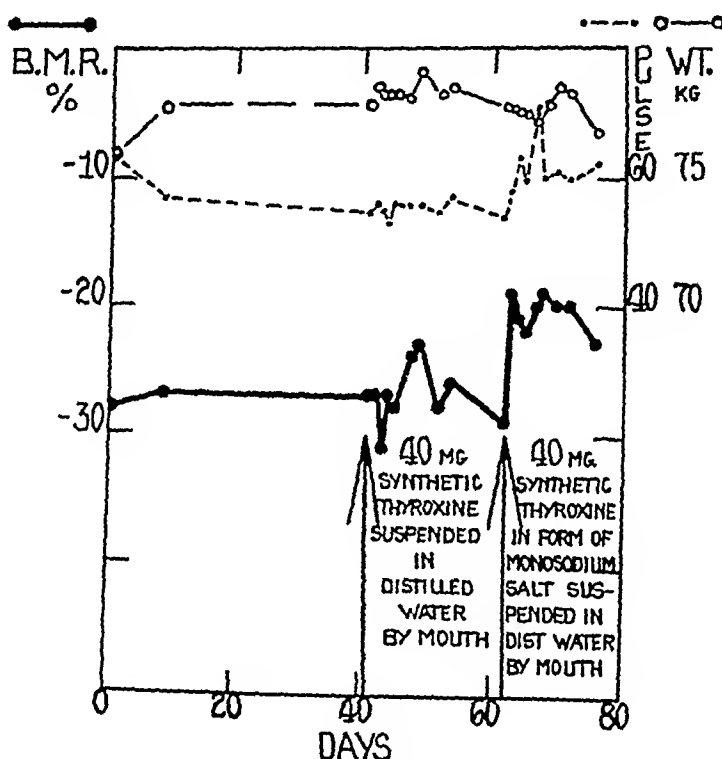


Chart 5 (Mrs J McH , height, 163 cm , age 42) —The oral dose of 40 mg of pure synthetic thyroxine was administered at 4 p m on Jan 31, 1933, in a suspension of distilled water, a total of 420 cc being used, largely for rinsing. The patient had been fasting since the preceding night. The oral dose of 40 mg of thyroxine in the form of its monosodium salt (41.2 mg of the salt) was given at 1 25 p m on Feb 21, 1933, in the form of tablets, which were washed down with 400 cc of distilled water. The patient had been fasting since the preceding night.

routes are summarized in table 2, where, in order to facilitate comparison, they have arbitrarily been calculated in terms of the effect of 10 mg of thyroxine by the method indicated in the footnotes. While the slight increase in basal metabolic rate caused by thyroxine as the free amino-acid is not regarded as definite, it may be noted that for every 10 mg of thyroxine administered by mouth in the form of the monosodium salt the

basal metabolic rate increased 7 points (from minus 28 to minus 21 per cent) on the average, for every 10 mg administered by mouth in alkaline solution the basal metabolic rate increased 20 points (from minus 31 to minus 11 per cent) on the average, and for every 10 mg injected intravenously in alkaline solution the rate increased 32 points (from

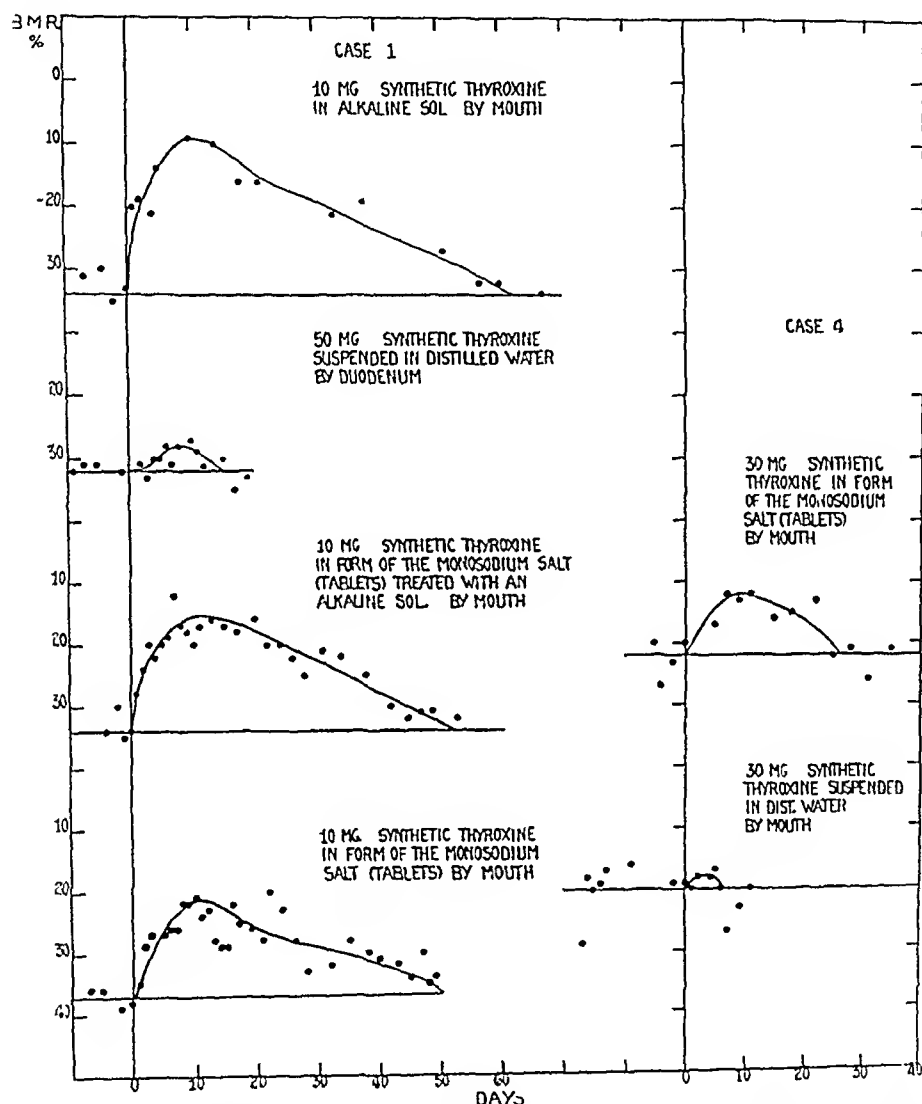


Chart 6—Detailed data for computing the excess basal calories produced by administering thyroxine in various forms by mouth and duodenum to patients 2 and 4

minus 37 to minus 5 per cent) on the average. Thus, thyroxine when administered by mouth in the form of the crystalline monosodium salt has only 35 per cent as much effect as when administered by mouth in alkaline solution and only 22 per cent as much as when it is administered intravenously in alkaline solution, while an alkaline solution is

only 63 per cent as effective when given by mouth as when given intravenously. These conclusions, of course, apply only to the administration of single large doses. The prolonged daily administration of small doses might produce somewhat different effects.

TABLE 2—Summary of Effects of Administering Thyroxine in Various Forms by Mouth and Duodenum Compared with Those of Administering It Intravenously in an Alkaline Solution

Medication*	Iodine Content of Substance Administered, Mg	Number of Patients	Number of Administrations	Average Basal Metabolite Rate Before Treatment, per Cent Normal	Average Level to Which Basal Metabolite Rate Rose, per Cent Normal	Average Change in Basal Metabolite Rate, Points	Average Change in Basal Metabolite Rate in Terms of Response to Intravenous Injection, per Cent†
10 mg pure synthetic thyroxine suspended in distilled water, by duodenum	6.5	3	3	—30	—29	1	3
10 mg † pure synthetic thyroxine suspended in distilled water, by mouth	6.5	4	4	—32	—30	2	6
10 mg § synthetic thyroxine in the form of its monosodium salt (tablets), by mouth	6.5	6	6	—23	—21	7	22
10 mg pure synthetic thyroxine in alkaline solution (sodium hydroxide), by mouth	6.5	5	5	—31	—11	20	63
10 mg ¶ pure thyroxine in alkaline solution, intravenously	6.5	6	8	—37	—5	32	100

* The effect of a given dose of thyroxine was calculated in terms of 10 mg by multiplying the number of points the basal metabolite rate changed following its administration by the fraction $\frac{10}{x}$, in which x = the dose of thyroxine used. All thyroxine referred to in this table was synthetic (Hoffmann-La Roche) except that so-called natural thyroxine (Squibb's) was used for four of the intravenous injections.

† For the calculation of the figures in this column the average change in the basal metabolite rate for each type of medication was divided by 32 and the result multiplied by 100.

‡ The patient not included in table 1 received a dose of 10 mg.

§ The two patients not included in table 1 received doses of 7.5 and 10 mg, respectively.

|| All doses were 10 mg except one of 7.5 mg. For the second patient of the present study we included for this summary of the effects of an alkaline solution by mouth only the effects of pure thyroxine dissolved in alkali, because of the uncertainty about all the monosodium salt being dissolved when the tablets of this substance were treated with alkali.

¶ All doses were 10 mg except two of 7.5 mg. The thyroxine was dissolved in an excess of sodium hydroxide for all injections except one, for which it was dissolved in an excess of potassium hydroxide.

COMMENT

The fact that the oral or duodenal administrations of single large doses of from 10 to 100 mg of pure thyroxine do not produce a measurable increase in basal metabolic rate is not proof that much larger doses would not have an effect. Data are now being collected on the first patient of this report which show that when a comparatively large amount of pure thyroxine is administered by mouth every day the basal metabolic rate may be held at the normal level. Final figures

are not yet available, but from data already collected, it would appear that the amount required for this purpose is about one hundred and fifty times as great as if the thyroxine were given intravenously in an alkaline solution. The great difference in the effects of the various forms of thyroxine by the oral route may be largely a matter of solubility, as previously suggested.⁶

Since thyroxine is soluble in alkali, it might be supposed that injecting it directly into the duodenum would result in some of it going into solution and hence being absorbed, because of the slight alkalinity of the duodenal contents. It would seem from our results, however, that this alkalinity is not great enough to result in the solution of more than a very small fraction of the amount administered.

SUMMARY

The oral administration of single doses of from 30 to 100 mg of pure thyroxine suspended in distilled water is without a definite effect on the basal metabolic rate in patients with myxedema.

The duodenal administration of single doses of from 10 to 50 mg of pure thyroxine suspended in distilled water is likewise without a definite effect.

From the data reported in this and two previous communications, it would seem that in patients with myxedema the oral administration of 10 mg of thyroxine in the form of its crystalline monosodium salt increases the basal metabolic rate 7 points (from minus 28 to minus 21 per cent) on the average, and the oral administration of 10 mg in alkaline solution increases the basal metabolic rate 20 points (from minus 31 to minus 11 per cent) on the average, while the intravenous administration of 10 mg in alkaline solution increases the basal metabolic rate 32 points (from minus 37 to minus 5 per cent) on the average.

6 Footnotes 1 and 2a

Book Reviews

Treatment in General Practice By Harry Beckman, M D, Professor of Pharmacology at Marquette University School of Medicine Second edition, revised and entirely reset Cloth Price, \$10 net Pp 889 Philadelphia W B Saunders Company, 1934

In looking over this compendium, the reviewer was impressed by its breezy style, its occasional personal opinion and its human quality. Having avoided books on therapy for many years, he was impressed by the amount of factual knowledge collected in these pages. Each disease is arranged in alphabetical order under subheads, which affords easy access to the matter in hand. The author has developed a distinct contribution to a book on treatment for quick reference. Having become interested in this style of presentation, the reviewer wandered into one of the most extensive county libraries in this country and asked the librarian about the former edition of the work. She stated that it is the most popular reference book on treatment on the shelves.

If any criticism might be made of this volume, it would be to advise the author to leave out all the tropical diseases which are not found in this part of the world. Adding references to the discussion would make the book too bulky. The names of authors are profuse enough in the text to permit more extensive reading.

The mass of data, observations, theories and polemics which make up medical literature is so vast—much being so inconsequential and much consisting of just words—that an effort of this kind, even though it must be revised as time goes on, is most commendable.

It is an excellent reference for general practice.

A Diabetic Manual for the Mutual Use of Doctor and Patient By E P Joslin Fifth edition Price, \$2 Pp 224, with 50 illustrations Philadelphia Lea & Febiger, 1934

In his usual lucid style Dr Joslin has incorporated the essential features of the modern treatment of diabetes in a very readable book of two hundred and twenty-four pages. Although the book is designed primarily for instruction of the patient, it is equally useful to the physician who does not limit his practice to diseases of metabolism. Dr Joslin's optimism and kindly interest in human beings is evident throughout. He understands diabetic patients as well as diabetes. He is fully aware of the many questions which arise to perplex the patient and answers these questions clearly and graphically. The book is illustrated liberally with photographs of diabetic patients enjoying life. Such photographs aid greatly in dispelling the horror of the disease so often encountered in dealing with patients who are beginning treatment.

The treatment of diabetes by diet is fully explained. Although the diets which the author recommends contain considerably more carbohydrate than those which he advocated in former years, none of his standard diets contain more than 172 Gm of carbohydrate. This figure is considerably lower than that recommended by the advocates of the "high carbohydrate diet." Perhaps as the result of his experiences before the introduction of insulin, Dr Joslin does not approve the use of diets low in carbohydrate and high in fat. He believes that these diets predispose to arteriosclerosis and the development of diabetic acidosis. In this respect his conclusions are at variance with those of some physicians in other clinics.

Numerous menus and recipes are given to exemplify the diets. A glance at the former is sufficient to indicate that the dietary life and consequently the social life of the diabetic patient today is much less ascetic than it was a few years ago. The work of the dietitian should be the expert and artistic application of the science of nutrition. The following menu, given for a lunch, illustrates how closely this ideal has been obtained: clear soup, steak, tomato and cucumber salad, peas, baked potato, butter, ice cream and saltines.

Since the introduction of insulin, diabetes has become a more chronic disease, and in consequence the incidence of degenerative complications appears to be

increasing. Considerable space in the manual is therefore given to the treatment of these complications and to their prevention by prophylactic hygiene. Careful study of these chapters, especially by middle-aged or elderly patients, would decrease greatly the needless occurrence of diabetic gangrene. The book is concluded with several interesting chapters on the heredity of diabetes, the relationship of diabetes to obesity, the treatment of diabetic children and the advisability of marriage of diabetic patients. The reviewer can recommend this book without qualifications.

Allergy in General Practice By Samuel M. Feinberg, Assistant Professor of Medicine and Attending Physician in Asthma and Hay Fever Clinic, Northwestern University Medical School. Price, \$4.50. Pp. 339, with 23 engravings and a colored plate. Philadelphia: Lea & Febiger, 1934.

In this book the author discusses the problems of allergy in a delightfully simple and straightforward manner. The book is evidently designed to stimulate readers interested in general medicine to realize that clinical allergy is frequently encountered, is recognizable and is often amenable to a fairly simple therapeutic program. It fulfils this purpose admirably.

The volume begins with an introductory chapter on the history of asthma and hay fever. There is next a short chapter dealing with the general principles of allergy and anaphylaxis, and then an excellent, more thorough discussion of asthma, with a consideration of its causes, diagnosis and treatment. The second half of the book deals with hay fever. O. C. Durham, chief botanist of the Abbott Laboratories, has contributed a chapter on the botanic aspects of hay fever, which will interest readers unfamiliar with such things as plants and pollens or the use of pollen surveys and weather maps in the treatment of hay fever. There is a short chapter on less clearly defined allergic conditions, such as eczema, angio-neurotic edema, gastro-intestinal allergy and allergic headache. Finally, the book closes with a group of thirty-nine case reports to illustrate certain principles of diagnosis and treatment outlined in the text.

The entire book is written clearly and is very readable. Each chapter ends with a good bibliography. Medical students and general practitioners will find this volume an excellent one for reference and study.

News and Comment

INTERNATIONAL CONGRESS OF GASTRO-ENTEROLOGY

The First Congress of Gastro-Enterology will be held at Brussels, Belgium, Aug. 8 to 10, 1935. The secretary-general of the Congress is Dr. George Brohee, Rue de la Concorde, 64, Brussels. Dr. Max Einhorn, 20 East 63rd Street, New York, has been asked to form, and to act as chairman of, the North American Committee, and Dr. De Witt Stetten to serve as secretary of the committee.

CORRECTION

In the article by Dr. M. M. Wintrobe on "Anemia," in the August issue (*ARCH. INT. MED.* 54:256, 1934), the fourth and fifth columns of section II in table 6 should read:

A Sudden loss of blood	Acute posthemorrhagic anemia
B Acute destruction of blood	"e g, hemolytic anemia caused by malaria"

In other words, "e g, hemolytic anemia caused by malaria" should appear on the third line opposite "B Acute destruction."

SPIDER POISONING

EXPERIMENTAL STUDY OF THE EFFECTS OF THE BITE OF THE FEMALE *LATRODECTUS MACTANS* IN MAN

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The belief that the bite¹ of the spider *Latrodectus mactans*,² common in the southern half of the United States (fig 1), is poisonous for man has been recognized for centuries³ Evidence for the truth of this belief has rested largely on the statement of patients that immediately prior to the onset of their symptoms they had been bitten by a spider answering the description of *Latrodectus mactans*⁴ In other cases, the spider alleged to have been responsible for the bite was caught and identified as a member of this species by competent arachnologists Many physicians accepted this evidence of their patients and reported cases of spider poisoning in the scientific literature

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1 Strictly speaking this spider does not "bite" at any time It pierces the integument of its victim by means of a pair of extremely sharp, chitinous claws (fig 3) articulating on the basal segments of the chelicerae The chelicerae are considered as modified antennae and constitute the first pair of appendages They lie in front of and are attached above the mouth parts Near the tip of each claw is a small orifice through which the venom from the poison gland is discharged in the wound The mouth parts are used only in pressing and sucking the fluid contents of the victim

2 This species possesses many scientific synonymous names (Petrunkevitch, Alexander A Synonymic Index-Catalogue of Spiders of North, Central and South America with All Adjacent Islands, Bull Am Mus Nat History 29 180 [May] 1911) and nicknames (Bogen^{5a}) Of the former, that most commonly used is "*Latrodectus mactans*", of the latter, "black widow" References in the literature are all in connection with the female of the species Little attention is given the male though it appears that it also possesses poisonous properties

3 (a) Merriam, C Hart The Dawn of the World, Myths and Weird Tales Told by the Mewan Indians of California, 1910, quoted by Comstock, J H The Spider Book, New York, Doubleday, Page & Company, 1913, p 359 (b) Robie, T An Instance of the Venom of Spiders, Phil Tr Roy Soc London 6:52, 1726, On the Effects of Inoculation, the , and the Venom of Spiders, Phil Tr Roy Soc London 7 20, 1724, quoted by Bogen^{5c}

4 Dorsal and ventral views of the adult female *Latrodectus mactans* are shown in the article on the "Life History of *Latrodectus Mactans*" in this issue (figs 1 G and H), p 844

Bogen,⁵ in a comprehensive review of the literature on this subject, has collected nearly four hundred cases of this kind, ranging from the year 1720^{3b} to 1931. Twelve cases in which a fatal outcome was attributed to the bite of this spider are included. Many other cases, as personal communications from local physicians testify, are never published, and, consequently, those reported represent but a small fraction of the actual number which have occurred. Since 1931 several authors⁶ have reported additional cases.

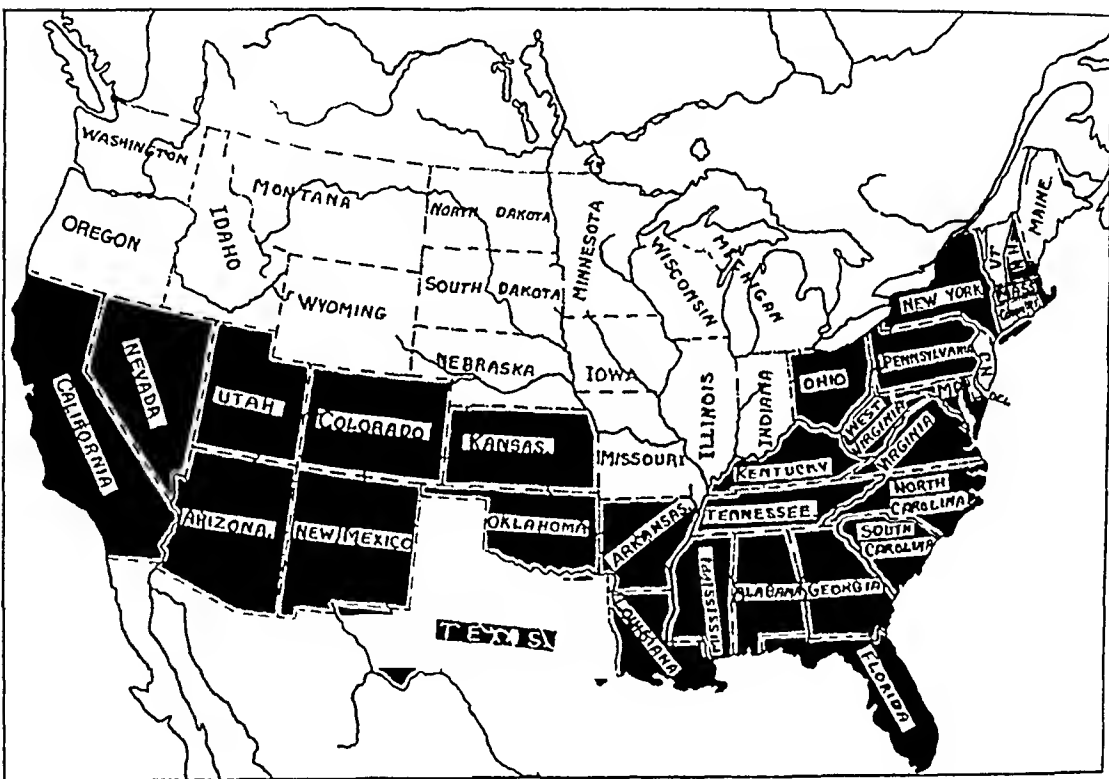


Fig 1—Distribution of *Latrodectus mactans* in the United States. The states in black are those in which, according to Bogen,^{5c} this spider has been found or from which bites have been reported.

5 (a) Bogen, Emil. Arachnidism. Spider Poisoning, *Arch Int Med* **38** 623 (Nov) 1926 (an excellent bibliography is given in the reprints), (b) Arachnidism. A Study in Spider Poisoning, *J A M A* **86** 1894 (June 19) 1926, (c) Poisonous Spider Bites, *Ann Int Med* **6** 375 (Sept) 1932 (note the additional bibliography on spider poisoning).

6 Combs, J. J. Spider Poisoning, *South Med & Surg* **94** 442 (July) 1932. Morton, C. B. Acute Abdominal Symptoms in Arachnidism, *Arch Surg* **26** 64 (Jan) 1933. Tolleson, H. M. Arachnidism, *J M A Georgia* **22** 30 (Jan) 1933. Walker, W. A. Arachnidism, *J M A Georgia* **22** 105 (March) 1933. Noland, L. Arachnidism, *Am J Surg* **20** 758 (June) 1933. Walsh, G., and Morgan, W. G. Arachnidism, *Am J M Sc* **186** 413 (Sept) 1933. Abrams, M. J. Arachnidism, *Bull School Med Univ Maryland* **18** 92 (Jan) 1934.

This evidence, coupled with similar reports on the poisonous properties of the several closely related species distributed around the world (fig 2), is strongly suggestive of the poisonous nature of this spider. Irrespective, however, of the integrity and intelligence of the patients thus bitten, such evidence remains essentially circumstantial in nature. As such, it affords some basis for the skepticism, so abundantly displayed

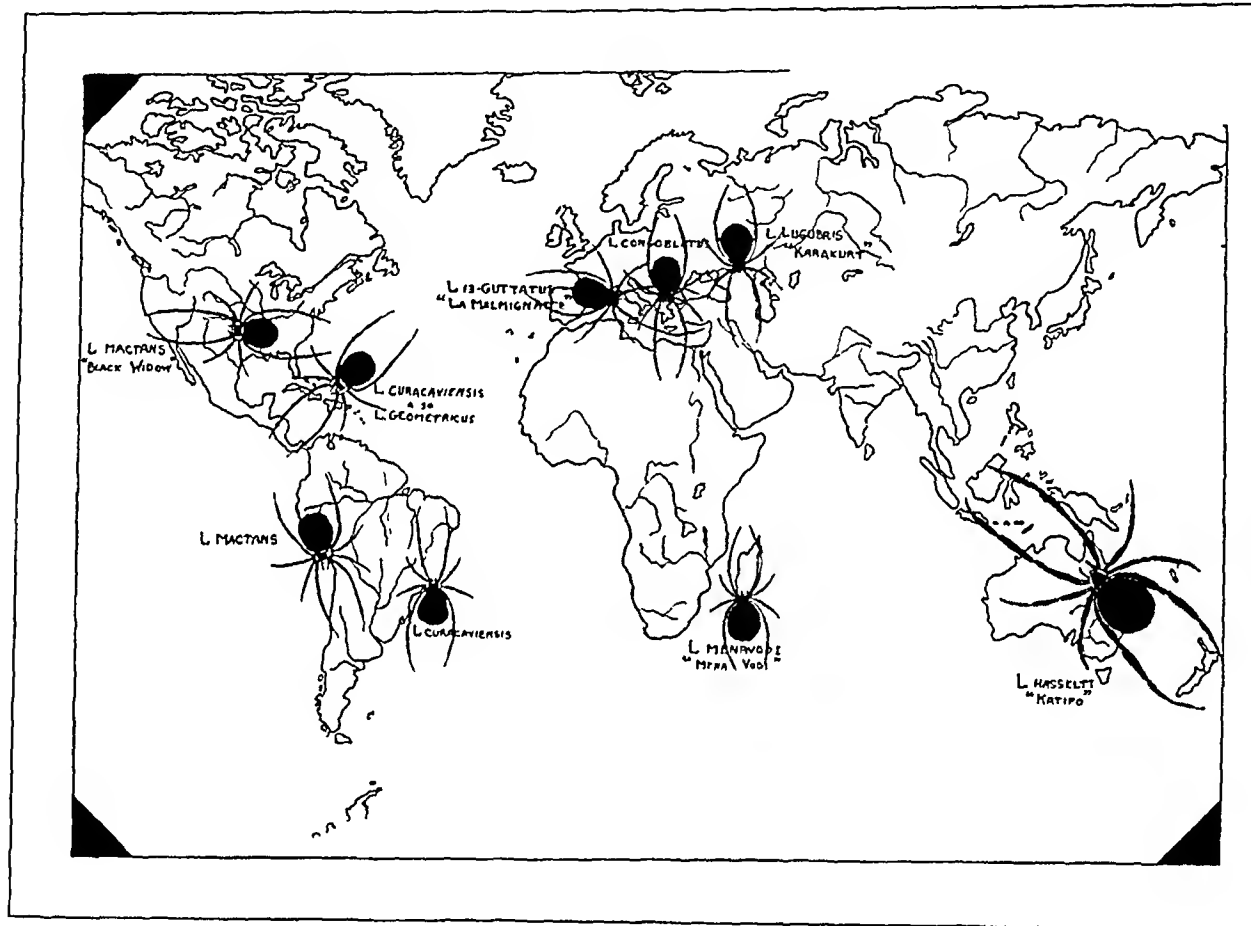


Fig 2—World distribution of genus *Latrodectus*. As this is based on the literature of *Latrodectus* poisoning, no attempt at absolute geographic exactitude in the distribution of each species has been made. Spiders of this genus are universally feared for the poisonous effects of their bite. The uncommon prevalence of local nicknames for these spiders is of interest.

in the literature,⁷ that so small and timid a creature could be capable of producing such severe general symptoms in man.

⁷ Van Hasselt, A. W. M. *Het spinnevergift*, *Nederl tijdschr v geneesk* 18 57, 1882. Emerton J. H. *Common Spiders of the United States*, Boston, Ginn and Company, 1902, p 124. Bogen.^{5a}

Further grounds for skepticism on the part of those who have had no intimate acquaintance with the effect of the bite of this spider are afforded in the conflicting results of experimental studies in animals and in man. Thus, Marx⁸ reported no effect in a guinea-pig following the bite of a mature female *Latrodectus mactans*. Escomel,⁹ on the contrary, reported marked symptoms, while Houssay¹⁰ and Troise¹¹ reported severe symptoms followed by death in many cases. Baerg¹² reported "moderately pronounced" symptoms in two rats in a series of four following the spider's bite, while Bogen¹³ reported marked symptoms with a high mortality in mice and in rats. Experimental



Fig 3—Adult female *Latrodectus mactans* dissected to show the two poison glands lying in the cephalothorax. The two chelicerae,¹ with their sharp, chitinous claws directed medially, are seen anteriorly lying between the palpi ($\times 10$)

8 Marx, George. On the Effect of the Poison of *Latrodectus Mactans* Walck. Upon Warm-Blooded Animals, *Proc Entomol Soc* **1** 85 (Oct 2) 1890

9 Escomel, E. Poisonous Spiders, *Rev Asoc med argent* **27** 853 (Dec) 1917, quoted by Kellaway, C H. Venom of *Latrodectus hasseltii*, *M J Australia* **1** 41 (Jan 11) 1930

10 Houssay, B A. Arañas Venenosas, *Conf Soc sud-am de hyg*, Buenos Aires **1** 545, 1917, quoted by Troise¹¹

11 Troise, E. Estudio farmacologico sobre la ponzoña del "*Latrodectus mactans*," *Rev Soc argent de biol* **4** 447, 1928, abstr, *Action pharmacodynamique du venin de Latrodectus mactans*, *Compt rend Soc de biol* **99** 1431 (Nov 9) 1928

12 Baerg, W J. Effects of the Bite of *Latrodectus Mactans* Fabr, *J Parasitol* **9** 161 (March) 1923

13 Bogen^{5a c}

studies¹⁴ show marked reactions in mice, rats, guinea-pigs and chickens. In mice the mortality was practically 100 per cent. Rabbits, cats, dogs and sheep seemed little affected. Experimental results with transplants and the injection of extracts of the poison gland (fig. 3) are likewise confusing and inconclusive.

Direct experimental evidence that the bite of *Latrodectus mactans* may be poisonous for man is furnished by the work of Baerig¹². On July 9, 1922, he placed one of these spiders on his little finger but could not induce it to bite. A further attempt with a second spider resulted in a bite, but the subsequent effect was local, mild and transitory. The following day the first spider was again placed on the finger and permitted to bite for five seconds. On this occasion severe aching pains in the muscles of the lumbar region, shoulders, chest and legs appeared, but Baerig concluded that the sharp pain in the finger and hand was the most prominent feature. The negative results of the first two attempts, however, together with the negative results of Lucas,¹⁵ Simon¹⁶ and Bordas¹⁷ following bites by *Latrodectus*, have in some measure detracted from the conclusiveness of his experiment. Bordas reported being repeatedly bitten on the hand by *Latrodectus tredecimguttatus* Rossi with no evidence of systemic poisoning. The *Latrodectus tredecimguttatus*, commonly known as "la malmignatte," is found in southern Europe (fig. 2) where it is regarded as poisonous to man, much as is the *Latrodectus mactans* in this country. Closely related though these species undoubtedly are, it is, nevertheless, hazardous to assume that experimental results with the European "malmignatte" would be equally applicable to the American "black widow"². Yet this assumption has, by inference, not infrequently been made¹⁸.

In a series of excellent articles Bogen⁵ has revived the interest of the medical profession of this country in the severe systemic symptoms resulting from the bite of *Latrodectus mactans*. Since experimental results in support of such a clinical entity have not been considered conclusive, an experimental study of the effects of the bite of this spider in animals and man has been made. The results in man, herewith submitted, emphatically support the contention of Bogen that arachnidism (spider poisoning) may be considered "a true clinical entity in the field of general medicine."

14 Blair, A. W. Effects of the Bite of the Female *Latrodectus mactans* in Animals, to be published.

15 Lucas, M. Ann. Entomol. Soc. de France, 1843, p. 8, quoted by Bordas¹⁷ Bogen^{5a}.

16 Simon, E. Histoire naturelle des araignees, Paris, 1882-1903, quoted by Bordas¹⁷.

17 Bordas, L. Recherches sur l'effet des piqûres du *Latrodectus 13-guttatus* Rossi ou Malmignatte, Compt. rend. Acad. d. sc. **133** 953 (Dec. 2) 1901.

18 Berland, Lucien. Le venin des Araignees, Rev. sc. **65** 267 (May 14) 1927.

EXPERIMENTAL BITE IN MAN

The subject of the experiment, begun on Nov 12, 1933, was a man (myself), aged 32, weighing 168 pounds (76.2 Kg), athletically inclined and in excellent health. The normal clinical findings in health had been recorded daily for one week prior to the bite. Reaction to bee stings and mosquito bites was normal.

The spider (no 11133) selected for the experiment, a mature female *Latrodectus mactans*,⁴ was found in a rock pile near my residence on October 25. Since then it had been kept in a jar in the laboratory. It was fed last (water beetle) on October 29. On the day of the experiment it was of moderate size, active and glossy black, with characteristic adult markings, and appeared to be in excellent condition.

10 45 a m With a pair of splinter forceps, the spider was gently grasped by the globose abdomen and applied to the medial surface of the terminal phalanx of the little finger of the left hand. The spider bit the moment it came into contact with the skin surface, twisting the cephalothorax from side to side as though to sink the claws of the chelicerae deeper into the flesh. The sensation resembled that of the prick of a very sharp needle, accompanied, however, by a burning sensation which increased in intensity during the biting period. The spider was permitted to bite for ten seconds. On its removal a small drop of a clear, whitish fluid, slightly streaked with brown, was observed at the site of the bite. This was allowed to remain untouched for one minute and was then wiped off with a cotton pledget. No definite marks of skin puncture were seen with the naked eye or with low magnification.

First Stage, Lymphatic Absorption—10 47 a m A bluish, pinpoint mark was seen at the site of the bite, surrounded by an area of blanching, 4 mm in diameter, a hot, burning sensation was present in the finger.

10 52 a m The area of blanching was more marked, the entire terminal phalanx was reddened, there was a throbbing, lancinating pain in the bitten finger.

11 00 a m Dull, aching pain was noted between the fourth and fifth metacarpophalangeal joints of the left hand with a slight numbness along the ulnar side of the hand, beads of perspiration were present at the site of the bite.

11 02 a m Dull, aching pain was present on the inner surface of the upper arm in the region of the superficial cubital gland (tenderness of this gland was still present two weeks after the bite), the terminal phalanx of the bitten finger was dark purplish red, slightly swollen and very painful.

11 05 a m Dull, aching pain was present in the left axilla, the whole arm had a dull, aching, slightly numb feeling.

11 07 a m Slight, aching pain was present over the lateral surface of the left side of the chest, pains in the axillary region now commanded more notice than the throbbing, occasionally lancinating pain in the finger.

11 18 a m Slight, aching pains were present over the precordium.

Second Stage, Vascular Dissemination—11 35 a m The blood pressure was 106 systolic and 78 diastolic, the pulse rate was 75 and weaker than normal, the respiratory rate was 16, and respiration appeared to be slightly deeper than normal, there was a dull, drowsy, lethargic feeling. This was the first circulatory (general) effect noted.

11 50 a m Slight, transient aching pains were noted in the epigastrium, there was a flushed, headachy feeling, the white cell count was 8,400, with 54 polymorphonuclears, 39 lymphocytes, 6 monocytes and 1 per cent eosinophils.

11 55 a m Definite, aching pains were present in the epigastrium.

12 00 a m Aching pains were present in the muscles of the neck, there was a feeling of general malaise, the blood pressure was 108 systolic and 82 diastolic, the pulse was weak, and its rate was 62

(From this stage on notes were taken by assistants)

12 10 p m Aching pains were present over the whole abdomen, the latter was tense, there was a flushed, trembly feeling in the legs

(At this time the subject was driven 3 miles to the hospital During the fifteen minutes thus taken the abdominal pains became rapidly more severe)

12 30 p m Severe, aching pain was present in the lumbar region, abdomen and chest, with a feeling of constriction in the latter, speech was difficult and jerky, respirations were rapid and labored, with a sharp brisk expiration accompanied by an audible grunt, the abdomen was rigid, the heart sounds were slow, regular and normal in character, the pulse was weak and thready, its rate was 60

(At this time two electrocardiograms were made These were found to be normal, differing in no essential from that taken several days prior to the experiment)

12 37 p m There were agonizing pains in the lumbar region, abdomen and chest, the abdomen was rigid, boardlike, with some tenderness in the epigastric region, the patient stated that it was torture to lie still on his back while the electrocardiograms were being made

12 45 p m The pains had spread to the legs, the patient lay on his right side with the legs, arms and body flexed, the respirations were labored, with a gasping inspiration and a sharp, jerky expiration accompanied by an uncontrollable, loud, groaning grunt

12 50 p m The patient was unable to straighten up or stand, showing almost rigid flexion of the legs, tremor, extreme ashy pallor and cold clammy sweat, with the general appearance of being in a condition of profound shock, he was undressed and placed in a hot bath, he stated that he experienced an immediate, appreciable diminution of pain and a sense of general relief The bitten finger was swollen, cyanotic, tender and painful

1 04 p m The pain, though partially relieved, was still severe, the respirations were still labored, spasm of the flexor muscles of the forearms and adductors of the thumbs ("accoucheur's hand") was present, a tingling sensation was felt in the hands and feet, the blood pressure was 75 systolic (no auscultatory diastolic reading was obtainable), the pulse was rapid, uncountable, weak and thready

1 15 p m The lips were tense and contracted, causing the mouth to assume an oval shape, the patient complained of slight dizziness and throbbing in the head

(Note by Dr J M Forney ¹⁹ "I saw the patient first at about 1 15 p m I found him in excruciating pain, gasping for breath and reclining in a tub of very warm water I do not recall having seen more abject pain manifested in any other medical or surgical condition All the evidences of profound medical shock were present")

1 30 p m The patient was removed from the bath and placed in bed, the face and body were very red, the respirations were still labored but definitely easier than prior to the bath

¹⁹ Dr J M Forney gave personal and professional aid during this experiment Figure 3 is a reproduction of a photograph by G G Goldenberg R O Griffith and E S Porter gave valuable assistance

1 45 p m The respirations had become increasingly labored and the pains more severe since removal from the bath, the patient writhed about on the bed, hot water bottles were placed to the abdomen and back, giving some relief from pain

1 52 p m The patient was perspiring profusely, the respirations were less labored, the blood pressure was 80 systolic and 50 diastolic, the pulse was weak, its rate was 120

Third Stage, Elimination—2 05 p m The patient stated that he felt a little better, he was given $\frac{1}{4}$ grain (0.16 Gm) of morphine hypodermically

3 40 p m The white cell count was 13,200 with 79 polymorphonuclears, 19.5 lymphocytes and 1.5 per cent monocytes

4 05 p m The patient vomited

5 25 p m A red streak extending up the back of the left hand from between the fourth and fifth metacarpophalangeal joints was noted

7 45 p m The patient was very restless, he still complained of severe pain in the abdomen, lumbar region and legs and of sharp intermittent pains in the bitten finger, he drank copiously and perspired freely, the eyes were red and watery and the face appeared swollen, the abdomen was still rigid, the blood pressure was 154 systolic and 92 diastolic, the pulse was stronger, its rate was 78, the respirations were shallow and still somewhat labored, the white cell count was 18,200 with 82 polymorphonuclears, 13 lymphocytes and 5 per cent monocytes

November 13 The temperature which was normal at the commencement of the experiment became from 1 to 2 degrees subnormal during the period of shock. On the afternoon of November 12 and during the night of November 12 and 13 it rose 1 to 2 degrees above normal. It had returned to normal by the morning of November 13 and remained so thereafter

The blood pressure reached its height the night of November 12. From that point it gradually fell, regaining normal limits by November 19

6 30 a m The patient was given a dose of magnesium sulphate

8 15 a m The patient stated that he spent a restless, sleepless, miserable night, perspiring freely and troubled by muscular pains and chilly sensations. Two tablets of a barbitol derivative with amidopyrine gave no relief. Several hot baths were given for relief of pain. On one occasion the patient stated that he became so upset mentally that he was afraid if firm control was not exercised he would go insane. Following this $\frac{1}{4}$ grain of morphine was given hypodermically

In the morning the patient complained of severe pains in the lumbar region and legs, the face had a swollen, puffy appearance, the eyes were red and watery, the abdomen was tense with slight epigastric tenderness

9 30 a m The urine showed a trace of albumin, a few pus cells, many red blood cells, epithelial cells and 25 blood and 5 granular casts under low power magnification. The white cell count was 19,150 with 77 polymorphonuclears, 18 lymphocytes and 5 per cent monocytes

(The polymorphonuclear leukocytes had returned to normal by November 15. No significant variations were noted in the erythrocyte counts or hemoglobin content. Unfortunately no counts were made during the stage of shock and no chemical studies were made on the blood)

4 10 p m The patient complained of pains in the back and legs, and of weakness and chilliness, the face was flushed and swollen, the tongue was heavily furred, and the breath was foul, the abdomen was tense, tremor of the hands and a papular eruption on the inner surface of the bitten finger and along the ulnar side of the hand were present, the patient had passed several liquid stools

8 00 p m The patient's condition was much improved, rheumatoid pains in the legs were now the chief complaint, he had drunk large quantities of orange juice all day and perspired freely

November 14, 8 00 a m The patient stated that he passed a very restless night, he ate toast and grapefruit for breakfast

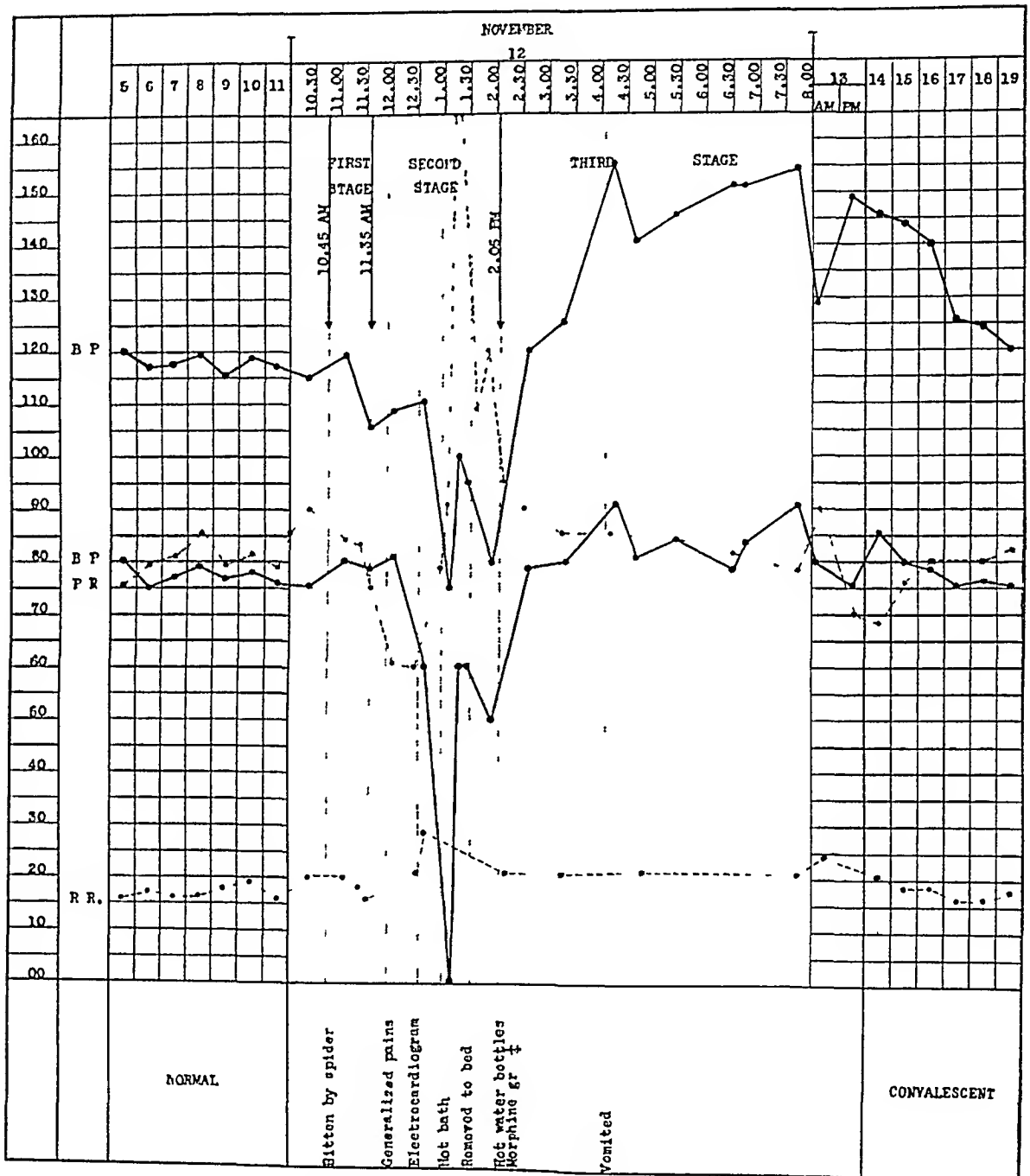


Fig 4—Clinical chart depicting the variations in blood pressure and in pulse and respiratory rate recorded during this experiment. The onset and duration of the three stages as observed in this case are depicted.

12 00 a m He stated that he was feeling much better, the chief complaints were rheumatoid pains in the legs and feet, chilliness, sweating and weakness, the face was less swollen, but the abdomen was still tense.

2 00 p m The patient walked to the bathroom unaided, the urine showed a trace of albumin, many pus cells, a few red blood cells and a few granular casts under low power magnification

(The urinary output was greatly reduced for the first five days following the bite The effect on the urinary output of the abnormal loss of fluid through intestinal and cutaneous elimination during this period must not, however, be disregarded The urinary output had returned to normal by November 18, coinciding with the cessation of excessive sweating)

November 15, 8 00 a m The patient stated that he slept at intervals during the night, the appetite was returning, rheumatoid pains in the legs and feet, chilliness and sweating of the legs and feet were the chief complaints, the abdomen was no longer tense and the face no longer swollen, the urine showed no albumin, few red blood cells, leukocytes, epithelial cells and numerous hyaline, granular and leukocytic casts

11 00 a m The patient was removed to his home by ambulance, he spent the remainder of the day in bed

Final Progress Note—From that time on recovery was rapid The pain in the bitten finger had disappeared by the evening of the second day following the bite A small, slightly tender, red papule was present at the site of the bite for two weeks, then disappeared The rheumatoid pains in the legs and feet had disappeared by November 20 Slight edema of the ankles was noted the first few days on moving about Urinalyses became normal on November 18 Generalized pruritus was present for some time, and desquamation of the hands and feet continued for about three weeks All the signs and symptoms had, however, disappeared by November 20 Subsequently the health of the patient has been excellent No sequelae have been noted to date (February 15, 1934)

COMMENT

A study of the clinical picture in this case indicates three well defined stages in its development Lymphatic absorption of the injected venom, as evidenced by the proximal progress of pain along the lines of lymphatic drainage, constitutes the first stage It is characterized by pains in the bitten finger and in the arm and by the absence of general systemic effects

Passing through the axillary lymph glands, the venom reaches the blood stream via the efferent axillary lymph channels, the subclavian lymphatic trunk and the subclavian vein This ushers in, secondly, the stage of vascular dissemination which is characterized, clinically, by the explosive onset of widespread agonizing muscular pains and a condition of profound shock This was, in this case, the most painful and critical stage, and yet no mention of a period of shock in this condition has so far been encountered in the literature Two possibilities may account for this discrepancy 1 All persons bitten may not receive a quantity of venom sufficient to induce the degree of shock obtained in this case 2 The patient may have recovered from the condition of shock before coming under medical observation

The third stage, that of elimination of the venom or its toxic products, commences with the rapid recovery from shock. It is characterized, clinically, by hypertension, diaphoresis, gradually diminished muscular pain, a slight rise of temperature, polymorphonuclear leukocytosis and urinary evidence of renal damage. This clinical picture, coupled with the slight headache and edema of the face and ankles, is very suggestive of the development at this stage of an acute (toxic) nephritis. The damage to the kidneys probably results from the attempted elimination of the venom or its toxic products by that route.

The condition of shock, characteristic of the second stage, suggests the possibility of the presence of a histamine-like ingredient in the venom of the spider *Latrodectus mactans*. Such a possibility is further suggested by the secretagogue action (salivation and lacrimation), evidence of contraction of the bronchial and intestinal musculature and symptoms of acute prostration and collapse which have been noted²⁰ in certain animals bitten by this spider. It is of interest that certain histamine-like properties of another secretion, crotalin (rattlesnake venom), have been observed experimentally.²¹

The question as to whether the agonizing muscular pains may play a part in the production of shock must also be considered. It is noteworthy, however, that the blood pressure had commenced to fall prior to the development of the acute muscular pains.

Although the mortality rate in this condition is low, I believe, as a result of my experience, that the possibility of a fatal outcome should by no means be disregarded. The second stage is to be regarded as the most critical, particularly in persons with conditions such as diabetes, chronic cardiac disease, alcoholism or renal disease, which predispose to shock.

The development in man during convalescence of any degree of immunity to the venom of this spider remains unproved. I was presented with the opportunity of deciding this point, but lacked the courage to submit myself to a possible repetition of the first experience. Degrees of immunity to the bite of this spider can be developed in animals²² and, on the assumption that man reacts likewise, convalescent serum has been used therapeutically. The results^{2c} so far obtained are, however, inconclusive.

Lacking the history of a spider bite, or an acquaintance with the clinical picture which it may produce, one might well be excused for mistaking the symptoms for one of several acute conditions. Thus a perforated peptic ulcer, acute pancreatitis, ruptured ectopic pregnancy,

20 Troise¹¹ Blair¹⁴

21 Essex, H. E., and Markowitz, J. A Comparison of the Physiologic Action of Crotalin and Histamine, *Am J Physiol* 92:705 (April) 1930

22 Baerg¹² Blair¹⁴

tabetic crisis, ruptured appendix with generalized peritonitis and renal or biliary colic may be considered in arriving at a diagnosis. Similarity between the clinical picture presented in poisoning by this spider and perforated peptic ulcer, particularly, has subjected the patient, on more than one occasion, to the added risk of surgical intervention²³

TREATMENT

Rational therapeutic measures in combating the effects of the venom injected by the bite of *Latrodectus mactans* should recognize the following points: 1 The reaction is due to the instantaneous injection, through a very minute skin puncture, of small quantities of venom, followed by rapid lymphatic absorption. 2 The subsequent vascular dissemination of the venom throughout the body may result in the development of a condition of shock. 3 Recovery involves the neutralization or elimination of the injected venom. 4 The development of an acute nephritis in the later stages is indicated.

The minute skin punctures, the rapid absorption and the small amount of venom capable of producing such a severe reaction in man make it unlikely that local applications can exert any appreciable neutralizing effect on the injected venom. A sharp "X" incision through the site of the bite, if made in the first few minutes after the accident, probably offers the best possibility for an early elimination of the venom.

Treatment of the shock as seen in the second stage of this condition involves the use of the accepted means for counteraction. Thus, the adoption of measures tending to a restoration of capillary tone and blood volume are indicated, while the use of cardiac stimulants is contraindicated. The use of large doses of alcohol for the relief of pain is to be condemned, in view of its tendency to accentuate and prolong the much more serious condition of shock. For the same reason, morphine, in the notoriously high dosages found necessary for relief of the associated agonizing muscular pains, should, at this stage, be used with caution. In my case immersion in a hot bath gave immediate and marked relief from pain. It may be merely a happy coincidence that it also marked the termination of the period of shock and the initiation of a progressive general improvement. Baerg¹² also remarked on the relief given by frequent hot baths, and it is said that in Russia baths are used extensively in the treatment of the bite of the closely allied species, the "Karakurt," found in that country.

In view of the clinical indications of the development of an acute nephritis, treatment during the third stage should be directed to giving

²³ Carrington, G. L. Bilateral Diaphragmatic Pleurisy Simulating Perforated Gastric Ulcer, *J. A. M. A.* 88:1395 (April 30) 1927. Bogen^{6c}

rest to the kidneys. On the assumption that the damage to the kidney arises during the elimination of the venom or its toxic products, the adoption of measures tending to aid in their possible elimination by other routes is indicated. The patient should be placed in a warm, well ventilated room, between woolen blankets and surrounded by hot water bottles. Frequent hot baths should be given. An intake of fluid sufficient to satisfy the patient's thirst should be encouraged, but in view of the damage to the kidneys fluids should not be forced. For the relief of pain and to secure rest, morphine may, at this stage, be used even in fairly high dosage. Spinal puncture is said to give considerable relief in many cases.^{5c}

The use of specific antivenins and convalescent serum in this condition must await the collection of further clinical and experimental data before the therapeutic value of these agents can be safely estimated.

CONCLUSIONS

1 The venom injected by the bite of the adult female spider, *Latrodectus mactans*, is dangerously poisonous for man.

2 The development of the ensuing clinical picture may be divided into three stages, of which the second, that of shock, is the most critical.

3 The sequence of symptoms following the injection of venom by *Latrodectus mactans* is sufficiently characteristic to entitle it to recognition as a clinical entity in the field of general medicine.

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LIFE HISTORY OF LATRODECTUS MACTANS

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In spite of the clinical importance of the bite of the *Latrodectus mactans* no complete study of its life history has so far been made. In view of this fact and since it is the only spider found in this country the bite of which has definitely been proved capable of causing severe¹ and, in some cases, fatal² systemic reactions in man, observations on its life history are of interest. The observations presented are based on a two year study of this spider as found in the vicinity of Tuscaloosa, Ala. It includes observations of the spider both in its natural environment and as raised in captivity.

APPEARANCE

The full grown female *Latrodectus mactans* (fig 1, *G* and *H*) has a large, globose abdomen attached by a slender pedicle to the much smaller cephalothorax. The body of an average-sized adult female is $\frac{1}{2}$ inch (1.27 cm) in length. The abdomen is $\frac{3}{8}$ inch (0.95 cm) in length and practically the same in width in the posterior third. When distended with food or eggs it overhangs the cephalothorax. The cephalothorax is $\frac{1}{8}$ inch (0.32 cm) in length and approximately the same in width at its broadest point. The slender, pointed legs when fully extended have a span of from $1\frac{1}{2}$ to 2 inches (3.81 to 5.08 cm). Laterally, they have a spread of $1\frac{1}{2}$ to $1\frac{3}{4}$ inches (3.81 to 4.45 cm).

The legs and body are a glossy black and as seen under the microscope are covered with short black hairs. On the ventral surface of the abdomen there is a rich red marking (fig 1 *H*) consisting of a rectangular bar from the center of which rises an inverted triangle. It is shaped somewhat like an hour-glass and stands out in striking contrast to the surrounding black. Dorsal to the spinnerets in the midline of the convex surface of the abdomen is an additional red marking (fig 1 *H*). These two markings constantly seen on the otherwise shiny black body are characteristic of the adult female and readily serve to distinguish this from other species of spiders. In immature females a broken row

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1 Baerg, W J. Effect of Bite of *Latrodectus mactans* (Fabricius), *J Parasitol* 9:161 (March) 1923. Blair, A W. This issue, p 831.

2 Bogen, Emil. Arachnidism, A Study in Spider Poisoning, *J A M A* 86:1894 (June 19) 1926, Arachnidism, *Arch Int Med* 38:623 (Nov) 1926. Poisonous Spider Bites, *Ann Int Med* 6:375 (Sept) 1932.

of red spots up the midline of the back is a constant finding. With the exception of the one above the spinnerets these gradually become suffused with black pigment and eventually disappear, though traces of them may remain in an apparently full grown female (fig 1 F)

HABITAT

The species *Latrodectus mactans* is found in North, Central and South America from New Hampshire south through Central America and along the west coast of South America to Tierra del Fuego. Of particular interest, however, is its widespread distribution throughout the southern half of the United States. It is very common throughout central Alabama. In this region the spiders are found in the angles between the roots of trees, beneath rocks, around old stumps, in holes in the ground and around houses and outbuildings. They have been found in the greatest numbers in the vicinity of human habitations. Occasionally they have been found in dark corners and in clothes closets in dwellings. In general they prefer dry, dimly lighted places.

WEB

The web is so distinctive that once it has been seen it may be recognized again at a glance. It is composed of very irregularly arranged, coarse threads which crisscross at various angles and in different planes. It is always found built in relation to a crevice or corner into which the spider, frequently by means of a poorly formed tunnel of silk, hurriedly retreats when disturbed. The web is relatively very strong and serves to entangle insects many times the size and weight of the spider. On many occasions I have observed large wood and water beetles and, in one case, a young mouse becoming entangled, swathed in silk and suspended in the web by these spiders. The web spun by the male is always smaller and weaker than that of the female.

FEEDING HABITS

When an insect becomes entangled in the web of the *Latrodectus mactans*, the spider, if not already fed to satiety, rushes out into the web to the immediate vicinity of the struggling victim. It then turns its back and, keeping at a safe distance, commences enswathing its prey in a mantle of silk. This is accomplished by the use of the long hind-legs which, in a rapid, alternate fashion, pull forth strands of silk from the spinnerets and cast them over the struggling insect. In the early stages of the struggle viscid silk³ is used, which by its viscosity and

³ Viscid silk, a transparent semifluid material, is characteristic of the family Therididae. It is thrown over the victim by the comb on the hind tarsi and is supposed to be derived from the lobed silk glands which have been found only in this family (Comstock, J. H. *The Spider Book*, New York, Doubleday, Page & Company, 1913, p. 333).

elasticity prevents any immediate escape. The victim's movements having then been further hampered by the addition of strands of fine silk, the spider approaches and seeks a point at which it may insert the claws of its chelicerae. This may be in the leg, the antenna or the body of the victim. The claws having been inserted and the venom thereby injected, the spider retires to await the result. In the space of a few minutes the struggles cease. The spider leisurely returns, completes enswathing the victim in silk and hoists the body to the desired position in the web. Fastening its mouth parts to some portion of the body the spider then proceeds to suck the body fluids. A small insect, such as a fly, may be sucked dry in a little over an hour. A larger insect, such as a water beetle, may be fed on for a day or two. The dry, skeletal husk is then cut out and dropped from the web. The abdomen of the spider after feeding may be twice its original size.

These spiders are capable of going without food for over a month with no recognizable harmful effect. Their fluid requirements are supplied by the body fluids of their victims. They seem to prefer to feed at night, though when hungry they feed at any time. They do not attack or feed on insects immediately preceding, during or immediately following a moult. On its completion they are, however, voracious and feed until the abdomen swells up to double its previous size. While awaiting their prey they are usually found hanging in their web with the ventral surface uppermost. They are cannibalistic, feeding on each other whenever the opportunity presents itself. The common nickname "black widow" given to the female of this species arose from her habit of capturing and feeding on the much smaller male.

MATING

Though the actual process of impregnation has not been observed it apparently occurs in the fall or early in the spring. This conclusion is based on two facts. First, mature males are most plentiful in the fall, becoming progressively less so during the following winter, spring and summer. Second, many females captured in the fall and kept alone in captivity over the winter lay fertile eggs the following spring. This suggests that, in most cases, the male impregnates the female in the fall and then dies or is killed during the following winter and spring.

EGG SAC

The egg sac is a globular or pyriform case of silk (fig 1 A) in which the eggs are loosely deposited. The laying of the eggs and the formation of the egg sac invariably took place at night. As a consequence the first steps in the formation of the egg sac have not been observed. In the early stages, however, it consists of a delicate, transparent mesh

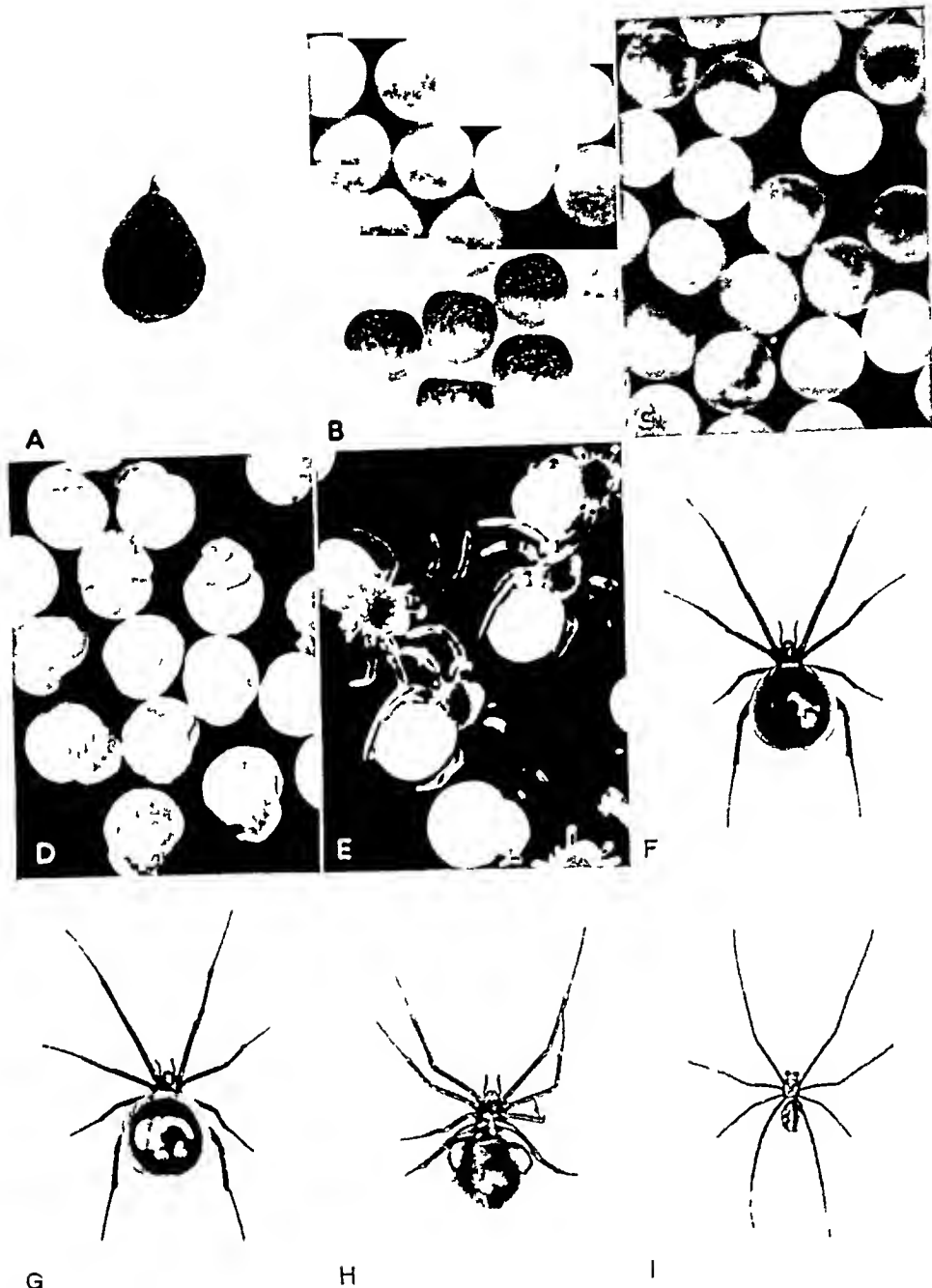


Fig 1—*A*, egg sac, reduced from $\times 1$ *B*, eggs, first day after laying, showing speckled appearance, reduced from $\times 10$ *C*, eggs, seventh day after laying, showing white discoid formation, reduced from $\times 10$ *D*, eggs, tenth day after laying, showing formation of cephalothorax. In some eggs the enveloping membrane has split, and the legs are beginning to emerge, reduced from $\times 10$ *E*, spiderlings emerged from egg membrane, eleven days after laying, reduced from $\times 10$ *F*, dorsal view of a large female which, although almost full grown, still has the red markings up the midline, reduced from $\times 1$ *G*, dorsal view of adult female showing the characteristic glossy, solid black appearance, reduced from $\times 1$ *H*, ventral view of adult female showing the characteristic red markings on the under surface of the abdomen, reduced from $\times 1$ *I*, dorsal view of adult male. Note the size relative to that of the adult female, the clear bands on the legs, the anteriorly placed genital bulbs and the characteristic abdominal markings, reduced from $\times 1$.

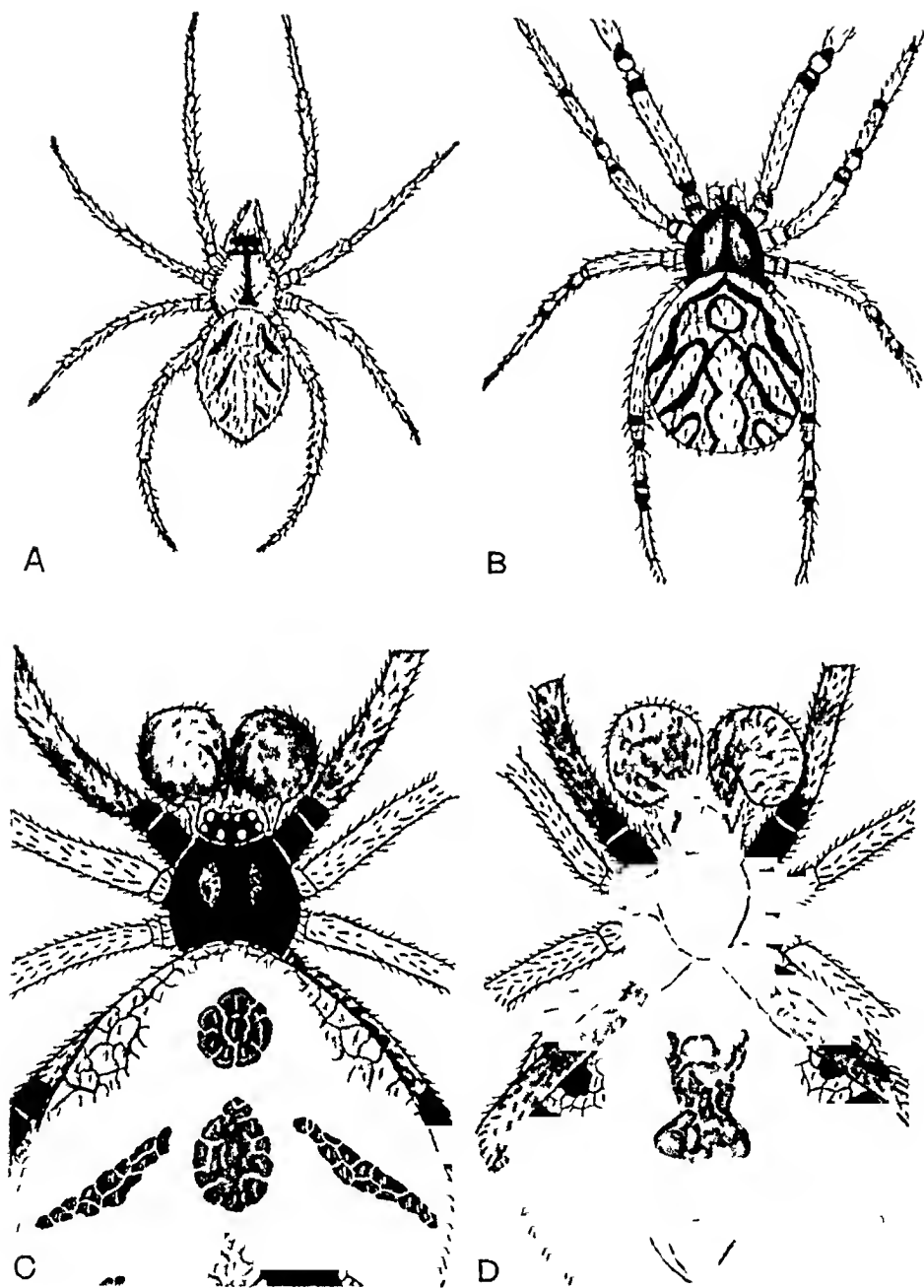


Fig 2—Series of spiderlings to demonstrate color development *A*, spiderling just prior to the second molt about the time of emergence from the egg sac, reduced from $\times 20$ *B*, spiderling twenty-one days later, just prior to the third molt At this time no distinction between male and female could be discerned, reduced from $\times 20$ *C*, dorsal view of spiderling immediately after the fourth molt The tibias of the palpi are now swollen to form the genital bulbs indicative of a male The color markings of both male and female spiderlings at this period are, however, the same These markings remain in the male but are lost in the female, reduced from $\times 20$ *D*, ventral view of spiderling as seen in *C*, showing color marking common to both male and female, reduced from $\times 20$

of silk through which the enclosed mass of eggs may be seen. The wall of the sac is then thickened and rendered opaque by a closely knit weave of fine viscid silk. The deposition of this viscid silk is accomplished by a rapid tapping action of the abdomen which brings the spinnerets situated at its tip into contact with the surface of the egg sac. The viscid silk hardens on drying, fixing the contour of the sac and producing an outer semirigid wall. The whole process from the laying of the eggs to the completion of the egg sac occupies less than twenty-four hours. The color of the egg sac is usually a creamy white when first formed, but darkens to a light tan with age. It hangs firmly suspended in the web by silken cords. The mother is usually found close by, with one or more legs placed protectingly on its surface.

The female *Latrodectus mactans* does not die after laying a mass of eggs and forming an egg sac. If well fed she may form a second egg sac filled with fertile eggs within nine days of the first. One female formed three egg sacs while under observation in captivity. Since one egg sac may contain over six hundred fertile eggs, the number of spiderlings which may arise from one female may number thousands. There is wide variation in the size of the egg sacs and the number of eggs contained.

EGGS

The eggs are round, translucent and approximately 1 mm in diameter (fig 1 B). The color of the eggs varies from a creamy white to a pale mauve. The cause of this variation was not determined and has no apparent significance for the course of future development. The eggs have a hard covering protecting the semifluid content and when dropped on a hard surface bounce and roll with no apparent injury. The number of eggs laid at any one time varies from less than one hundred to more than six hundred. The chief egg-laying season is spring and early summer, though so long as the weather remains warm, fresh egg sacs continue to be formed by newly matured females.

The eggs of *Latrodectus mactans* are very poisonous. Two eggs crushed and emulsified in a drop of saline solution were found sufficient to kill an adult white mouse when injected intraperitoneally. A few drops of a saline emulsion of eggs injected intravenously kills a rabbit in two minutes.

DEVELOPMENT

The eggs when first laid are speckled with flecks of a white flocculent material (fig 1 B) lying in the semifluid egg contents immediately beneath the transparent egg covering. During the next few days this material coalesces to form a white, discoid mass near the upper surface of the egg (fig 1 C). Approximately ten days after the eggs have been laid this mass suddenly enlarges and projects as a knob from the globular

surface of the egg. The membranous covering of the egg becomes wrinkled in this region, and beneath it the outlines of the cephalothorax and appendages become clearly discernible. By the following day the enlarging cephalothorax has split the membranous egg covering (fig 1 *D*). The split enlarges, and in twenty-four hours the spiderling emerges (fig 1 *E*). During the hot summer weather ten or eleven days is the average period for hatching. Cold weather, however, lengthens the period, and if the cold is sufficiently severe or prolonged, hatching may never occur.

Subsequent development of the newly hatched spiderlings is marked by a series of moults accompanied by a gradual increase in size and in pigmentation. The early modification of the palpi to form secondary sex organs serves to differentiate the male from the female.

After hatching the spiderlings remain in the egg sac. There they undergo their first moult approximately five days later. Prior to this movements are feeble, hairs are absent, and pigmentation is scanty. Following the first moult the spiderlings become increasingly active and finally, after making a pinhole opening in the egg sac, emerge one by one, spinning a fine web as they go. In warm weather this process takes place about twenty-five days after the eggs are laid. The second moult takes place outside the egg sac a few days after the spiderlings have emerged. When they first emerge from the egg sac they cluster in their finespun web, but after the second moult they commence to separate and seek a home for themselves.

Prior to the second moult nourishment for their growth is provided by that already present in the globose abdomen. After the second moult, however, this source is depleted as evidenced by the shrunk abdomen, and they commence to attack and to feed on one another unless more accessible food is available. The mother of the brood makes no attempt to provide them with food and may herself feed on them. The mortality rate is thus very high.

Six moults are usually required for complete development. The interval between moults varies with the amount of food available. In the early stages of development the food supply being nearly equal for all the interval is correspondingly more uniform. Later, however, the wide variations in the food supply of each spider produce a corresponding irregularity in the moulting intervals. In the early stages the interval is usually from fifteen to twenty days, but later it may be a month or more.

The cephalothorax and appendages of the newly hatched spiderling are crystal white (fig 1 *E*). The globose abdomen may be creamy white or reddish brown. It is flecked with white flocculent masses which early become collected on the ventral surface, down the midline of the dorsal surface and in stripes on the side of the abdomen. As

growth proceeds an orange and later a red color appears in these regions. The rest of the body in the meanwhile becomes gradually suffused with a black pigment. This pigment first appears on the region of the ocular tubercle, the region around the spinnerets, the tips of the chelicerae and mouth parts, down the midline of the dorsal surface of the cephalothorax and on the tips and joints of the appendages (fig 2 *A* and *B*). Prior to the fourth moult no indication of the sex of the spiderling is furnished by the color markings or external structures. The color markings of the spiderlings are retained in large measure by the adult male. Thus the male has, in addition to the red, ventral, abdominal marking, common to both sexes, a row of orange red spots down the midline of the dorsal surface of the abdomen, three orange-yellow side stripes on the abdomen and clear straw-colored bands on its legs (fig 1 *I* and fig 2 *C* and *D*). All these color markings are likewise possessed by the immature female. Later, however, they are lost in a general suffusion of black pigment, only the ventral red marking and that over the spinneret remaining in the adult female (fig 1 *G* and *H*).

At the fourth moult the tibia of the palpi of a male spiderling suddenly expands to form a yellowish or olive green bulbous structure (fig 2 *C* and *D*). This swelling involves to a lesser extent the tarsus and the patella. The tarsus appears as the pointed extremity and the patella as the expanded cap of the bulb. After the fourth moult, though the color markings of male and female may be similar, the modification of the male palpi to form secondary sex organs serves as an infallible guide to the sex of the spider. At the fifth moult the secondary sex organs of the male undergo a second remarkable transformation. In place of a rounded bulbous structure a complex structure with a spiraled cuplike opening appears. It is used for the storage and later the transference of seminal fluid to the spermathecae of the female at the time of mating. With its appearance the male may be regarded as an adult, though further increase of size occurs. The development of these adult sex organs is attained in from two to three months. The maturation of the male is somewhat more rapid than that of the female.

SPAN OF LIFE

The life span of the female is approximately one year. If hatched early in the spring the spiderling may, if the food supply is adequate, mature by late summer, live over the winter, lay its eggs the following spring and die during the summer or fall.

The life span of the male is usually less than a year. If hatched early in the spring it matures during the summer, mates and dies during the fall or winter.

DANGER TO MAN

In man the bite of *Latrodectus mactans* is followed, with dramatic suddenness, by a characteristic and alarmingly severe systemic reaction ⁴ The full grown female, particularly when distended with eggs, appears from experiments with animals, to be the most poisonous It is, however, a timid creature and when disturbed makes every attempt to escape This explains the relatively small number of bites in spite of the prevalence of these spiders in this section When cornered or compressed, as between the skin and clothing, the spider bites in self-defense Bites about the genitals are frequent on persons using an outdoor privy across the seat of which one of these spiders has spun its web The frequency with which "the black widow" is found around and in human habitations constitutes a potential danger The male, though also poisonous, may, on account of its size, greater timidity and scarcity, be ignored as an etiologic factor of any importance in arachnidism

SUMMARY

Latrodectus mactans is the only proved poisonous spider found in the United States No complete study of its life history has, however, so far been made For the past two years a study of this spider as found in the vicinity of Tuscaloosa, Ala., has been made Observations, accompanied by illustrations, on its appearance, habitat, web, feeding habits, mating, egg sac, eggs, development, span of life and danger to man are presented

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4 Baerg ¹ Blair ¹ Bogen ²

PERNICIOUS ANEMIA

RESULTS OF TREATMENT OF THE NEUROLOGIC COMPLICATIONS

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AND

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CHICAGO

The introduction of liver for the treatment of pernicious anemia by Minot and Murphy has provided an efficacious method of increasing the number of red blood cells and the percentage of hemoglobin to figures approaching normal, thereby relieving the general asthenic symptoms and prolonging the lives of patients indefinitely. The effect of liver on the neurologic complications of pernicious anemia also has been studied with great interest, but with the use of less certain criteria on which conclusions may be based. The literature already contains reports of several studies carried out over long periods of time which seem to indicate both prophylactic and curative values of liver extracts on the neurologic complications. However, some clinicians attributed an indirect action to the liver and suggested that the usual gain in general strength enhances the patient's powers of compensation for his neurologic defects, while others denied any noteworthy change in the nervous symptomatology. Perusal of the published data reveals an almost complete absence of adequate neurologic studies of patients over a long period of time. In many instances only one careful neurologic examination was performed, or observations before and after therapy were not made by the same examiner.

In 1927, Koessler and Maurer¹ used a diet which was rich in vitamins A, B and C for the treatment of pernicious anemia, but which was virtually liver treatment because from 100 to 250 Gm of liver was prescribed daily to insure an adequate supply of vitamin A. From the practice of one of us (R R G) 2 patients were reported in whom striking improvement occurred, so that they were able to walk after a fashion although they had previously been bedridden. Improvement

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1 Koessler, K K, and Maurer, S. The Treatment of Pernicious Anemia with High Caloric Diet Rich in Vitamins, J A M A 89-768 (Sept 3) 1927

in strength and ability to get around was not accompanied by noteworthy change in the objective neurologic status

Bubert² reported a case frequently quoted as showing neurologic regeneration induced by the use of liver. The description of the course of the nervous symptoms and signs included not only contradictions but also evaluations of the effects of therapy by neurologists who had not examined the patient before. The objective evidence of improvement consisted largely in the return of knee jerks, while at the same time the abdominal and cremasteric reflexes were lost, obviously suggesting not improvement but progression of the lesion to the lateral tracts. The case of Mason³ is another example of poorly controlled observations on the changing neurologic status, and yet it was used as evidence of possible improvement of cord symptoms by treatment.

Richardson⁴ recorded 67 cases of pernicious anemia, 14 of which showed ataxia. Seven of these he considered as showing severe cord changes. "The patient's statement as to his ability to get around and do his work was taken as evidence of improvement, even though the objective signs might still be present." On this basis 8 patients with ataxia were moderately improved and 2 showed no change. Starr⁵ reported 8 cases of combined degeneration of the spinal cord which had been studied for three years. On adequate liver therapy, with the blood count maintained at a high level, the condition in 4 cases remained stationary and showed no increase in neurologic signs. A like number in which the blood count was always low showed progressive neurologic changes. The conclusion was drawn that adequate liver therapy may have a preventive effect on degeneration of the cord.

Minot and Murphy,⁶ in a discussion concerning 105 treated patients, stated that it was their experience that neural symptoms developed in few patients receiving therapy and that no extension or aggravation of a preexisting lesion occurred after one month of therapy. They quoted 2 exceptions, cases in which the involvement of the spinal cord was extreme but ascribed to neglect of diet. "Of course changes in reflexes have remained present," they stated. Coordination of the extremities had distinctly improved in many cases but Minot and Murphy stated that although neurologic improvement has occurred with liver therapy, the ability to walk after having been bedridden was prob-

2 Bubert, H. M. Subacute Combined Sclerosis. *J. A. M. A.* **90**: 903 (March 24) 1928.

3 Mason, E. H. Pernicious Anemia. *J. A. M. A.* **90**: 1527 (May 12) 1928.

4 Richardson, E. Pernicious Anemia. *New England J. Med.* **200**: 540, 1929.

5 Starr, P. The Prevention of Spinal Cord Degeneration in Pernicious Anemia. *J. A. M. A.* **96**: 1219 (April 11) 1931.

6 Minot, G. R., and Murphy, W. P. A Diet Rich in Liver in the Treatment of Pernicious Anemia. *J. A. M. A.* **89**: 759 (Sept. 3) 1927.

ably due to improvement of muscular strength from a continuously high level of red blood cells. In summary they stated "Improvement in neural symptoms has been most gratifying to the patient," and such symptoms had not definitely progressed or developed under adequate dietary treatment (200 Gm or more a day)

Smithburn and Zerfas⁷ reported a study of 115 cases of pernicious anemia. The mental condition improved rapidly on liver therapy although a few patients persisted in having ideas of persecution over a period of several months. These workers observed that no tendon reflexes changed while the patient was under treatment, except that in several instances diminished reflexes disappeared entirely, but when hyperactive, the reflexes remained so or became progressively worse. Improvement was seen most frequently in paresthesia. Improvement in ataxia, sphincteric control and psychic changes was considered the result of betterment of the muscular strength and general condition due to the normal blood range, especially since in 13 cases ataxia was unaccompanied by any other defect and was attributable to weakness rather than to a central lesion. Davidson, McCrie and Gullard⁸ expressed the opinion that symptoms referable to the nervous system if of recent date and in the nature of mild paresthesia may completely disappear. However, when they are the result of actual destruction of the nerve tissue no cure can be expected.

Sturgis, Isaacs and Smith⁹ stated that in a series of patients with pernicious anemia with signs and symptoms of combined or lateral degeneration of the cord the administration of liver or liver extract produced no change in neurologic signs, although regeneration of the blood followed the usual course. However, early signs of involvement of the cord were followed by improvement after treatment with liver and physical therapy. The latter procedure was designed to strengthen the muscles and develop their control. Sturgis and Isaacs¹⁰ stated elsewhere that patients with paresthesia are often helped by liver and ventriculin therapy. "In general it may be concluded that improvement in the minor neurological symptoms frequently occurs, but in patients with more extensive involvement the outlook is far less promising."

7 Smithburn, K. C., and Zerfas, L. A. Neural Symptoms and Signs in Pernicious Anemia, *Arch Neurol & Psychiat* **25** 1100 (May) 1931

8 Davidson, G., McCrie, J. G., and Gullard, G. L. The Treatment of Pernicious Anemia. Liver Diet. *Lancet* **1** 847, 1928

9 Sturgis, C. C., Isaacs, R., and Smith, M. The Treatment of Pernicious Anemia with Liver Extract, *Ann Int Med* **1** 994, 1927

10 Sturgis, C. C., and Isaacs, R. Clinical and Experimental Observations on the Treatment of Pernicious Anemia with Desiccated Stomach and with Liver Extract. *Ann Int Med* **5** 131, 1931

In 1930, Baker, Boidley and Longcope¹¹ reviewed the histories of 44 cases of pernicious anemia of which 39 showed evidence of involvement of the nervous system. The patients were studied during varying periods of liver therapy ranging from six to forty months. Improvement was reported in 61.5 per cent and no improvement in 36 per cent. The percentage of improvement was much higher in a group of patients treated longer than six months. Evidence of improvement cited included diminution of paresthesia, a change from ataxic to normal gait, a decrease in sphincteric disturbances, the disappearance of spasticity, the recovery of cutaneous sensibility and a change in the Babinski response from positive to "improved." Reduction in the quantity of liver ingested resulted in the relapse of the organic neurologic signs.

Ungley and Suzman¹² reported 61 cases of pernicious anemia with degeneration of the cord, 30 of the patients were treated with liver and compared with 31 who were observed for two years prior to the "liver period." Of the untreated patients none improved, 3 showed progression and 28 died. Of those treated with liver, 17 improved, in 8 the condition remained stationary or became worse, and 5 died. Numbness and tingling disappeared in practically all cases. The Babinski responses were lost in 5 cases, cutaneous sensation became normal in 8 and sphincteric disturbances disappeared in 6. The authors called attention to the phenomenal response of the nervous system to therapy on the twelfth day of the initial liver treatment. This is, of course, the time when the increase in red cells manifests itself in increased general strength and power of the patient. Nevertheless, the authors stated their belief that liver has a specific effect on the lesions of the cord caused by pernicious anemia.

Farquharson and Graham¹³ reported 18 cases exhibiting well defined signs of subacute combined degeneration. They concluded that "adequate liver therapy has a specific effect on the nervous system lesions, arresting their progress in virtually all cases and causing marked improvement in large numbers." However, complete recovery had not occurred after definite nervous manifestations, "but liver extract not only cures the anemia but prevents the subsequent development of subacute combined degeneration of the cord. It arrests the progress of existing nerve lesions and in many instances results in marked improvement of the nervous signs and symptoms, more particularly those of

11 Baker, B. M., Boidley, J., and Longcope, W. T. The Effect of Liver Therapy on the Neurologic Manifestations of Pernicious Anemia, *Am J M Sc* **184** 1, 1932.

12 Ungley, C. C., and Suzman, M. M. Subacute Combined Degeneration of the Cord. Symptomatology and Effect of Liver Therapy, *Brain* **52** 271, 1929.

13 Farquharson, M. B., and Graham, D. Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, *Canad M A J* **25** 237, 1930.

relatively short duration" Under the improved organic signs the authors included paresthesia, objective sensory changes in reflexes, ataxia and signs of disease of the pyramidal tract Progress of the neurologic defect was attributed to an insufficient quantity of liver (an adequate dosage was considered to be the juice from 1 pound [453 Gm] of liver a day) The greatest improvement in neurologic signs and symptoms occurred after the second month of therapy The authors did not agree that general improvement of strength could account for the striking improvement in the neurologic states of their patients

The obviously conflicting reports concerning the effect of the feeding of liver on the neurologic complications of pernicious anemia stimulated us to organize a special clinic for the study of such cases at the University of Chicago In the two and a half years of operation there have been studied in our clinic over 50 cases of combined degeneration of the cord and numerous cases of pernicious anemia uncomplicated by neurologic lesions

Most of the patients were first hospitalized for a month and given liver extract or ventriculin in order to raise the blood count rapidly After discharge from the hospital, varying amounts of liver extract or the domestic extract of liver were given The term "adequate therapy" used throughout the paper is understood to mean a sufficient quantity of liver to maintain a normal blood level together with that feeling of well-being peculiar to health This has at times meant a change in the amount of liver given, as indicated in the table as the average dosage for the period Many patients during epidemics of colds required additional liver, while several whose blood value had been slightly over the normal level complained of heaviness with an annoying hot sensation, requested a reduction in the intake of liver

We have in most cases not otherwise indicated given the lowest level of the red cell count for the period after the blood once reached normal limits The patients for the most part were able to maintain a red cell count within a few hundred thousand on either side of the accepted normal limits

Careful neurologic reexaminations were made at regular intervals, often twice a month or, as time went on, once a month The cases reported here were selected from those of undoubted pernicious anemia showing variable degrees of anemia, an atrophic tongue, achlorhydria, as demonstrated by the histamine test, and a typical blood smear

UNCHANGED CASES

In the table are outlined the essential neurologic data concerning 19 cases of pernicious anemia with complications referable to the nervous system The ages ranged from 37 to 73 years Among the findings were signs and symptoms referable to the posterior and lateral columns

Data on Nineteen Cases of Combined Degeneration of the Cord Treated with Liver Without Change in Neurologic Status

Case	Age and Sex	Previous Duration	Weakness	Dyscathasias	Red Blood Cells, Hemoglobin	Myoclonic Tone	Deep Reflexes in the Legs	Babinski Reflex	Clonus	Position Sense	Vibration Sense	Cutaneous Sense	Ataxia	Romberg Sign	Liver Therapy
1	60 M	2 months Sudden onset	+	+	1,350,000 50%	—	Decreased	—	—	Poor in feet	Dim below 12th dorsal	Hyperalgesia in legs	+++	+	1 lb daily from Nov 2, 1931, to Jan 10, 1933 red cell count, 4,100,000, hemoglobin, 83%
2	55 F	2 years Irregular liver therapy for 14 mos	+	+	2,080,000 70%	—	+++	+	+	Poor in legs	Absent below patella	—	—	+	Domestic extract, 1 lb daily for 6 mos, red cell count, 4,800,000, hemoglobin, 101%
3	47 M	1 year	+	+	5,010,000 90%	Increased	++++	—	—	—	Diminished	Decreased in legs	++	+	1 lb daily for 15 mos, main tained count
4	7 F	1 years	—	+	4,500,000 57% (for 2 yrs)	Spastic legs	++++	+	+	Decreased in feet	Decreased in feet	Hyperalgesia in hands	+	+	1 lb daily for a total of 3 yrs
5	47 M	6 months Treated as tabes dorsalis	+	+	1,400,000 57%	—	Achilles 0 knee jerks unqual	+	—	Decreased	Decreased	—	+	+	Daily for 22 mos, reflexes became exaggerated, red cell count, 4,700,000, hemoglobin 94%
6	59 F	7 years Diagnosed as pernicious anemia	+	+	4,500,000 60%	—	Achilles 0 knee jerks decreased	+	—	Decreased	Absent below knees	—	+	+	1 lb daily for 2 yrs, main tained count
7	60 F	5 years Irregular liver therapy	+	—	3,500,000 67%	—	Decreased	+	—	Decreased	—	—	—	+	1 yr and 8 mos, red cell count, 4,300,000, hemoglobin, 80%
8	63 M	6 weeks	—	+	3,180,000 67%	—	Decreased	+	—	Decreased in legs	Decreased in legs	Decreased in hands	—	+	15 mos, red cell count, 4,400,000 hemoglobin, 83%
9	59 M	2 years	+	+	4,100,000 87%	—	—	+	—	—	Deficient	—	—	—	27 mos, 3 vials of oral extract daily
10	64 M	6 months	—	+	4,000,000 62%	Spastic	+++	—	—	—	Absent in legs	—	++	++	32 mos 3 vials of Lilly's oral extract daily, red cell count 4,900,000, hemoglobin, 100%
11	64 M	2 years	+	+	2,200,000 53%	Slightly spastic	Decreased	+	—	Decreased	Decreased	—	Slight	+	29 mos, red cell count, 4,100,000, hemoglobin, 75%
12	70 M	2 months	+	+	3,900,000 66%	—	—	—	—	Decreased	Decreased	Hyperalgesia in fingers	—	+	26 mos, red cell count, 4,400,000, hemoglobin, 90%
13	64 M	4 months	+	+	3,100,000 85%	—	—	—	—	—	Decreased	Hyperalgesia in fingers	—	—	6 mos, red cell count, 4,700,000 hemoglobin, 92%
14	58 F	18 months	+	+	2,080,000 51%	Spastic	+++	—	—	Poor	Absent below 7th dorsal	—	+	+	6 mos, red cell count, 4,100,000, hemoglobin, 80%
15	49 M	4 years	+	+	3,400,000 84%	Spastic	+++	+	+	Absent in legs	Lost below 12th dorsal	Decreased in fingers and legs	+	+	19 mos, red cell count, 4,700,000, hemoglobin, 92%
16	44 F	4 years	+	+	4,000,000 91%	—	+++	—	—	Decreased	Decreased	—	—	—	6 mos, red cell count, 4,980,000 hemoglobin, 97%
17	66 F	2 years	+	+	1,700,000 34%	Increased	+++	—	—	Absent in feet	Absent below knees	—	—	+	6 mos, red cell count, 4,300,000 hemoglobin, 73%
18	49 M	2 years	+	+	1,900,000 78%	—	+	—	—	Decreased	Decreased	—	—	+	2 yrs and 6 mos
19	54 M	6 weeks	+	+	3,200,000 60%	—	+++	+	—	Reduced in feet	Reduced below knees	—	—	—	2 yrs, red cell count, 4,800,000, hemoglobin, 93%

and varying combinations of these. The patients were treated with a pound of liver or a domestic extract of liver daily for from six months to three years. In all, the blood count and hemoglobin percentage were maintained at a high level. However, in none of these cases was there the slightest change in any sign of organic disease, including the great variety of signs which have been reported as improved under therapy by other observers.

In those in whom the blood count was low at our first observation therapy resulted in a concomitant increase in general strength, but not the slightest effect on the neurologic signs was noted.

CASES PROGRESSING UNDER THERAPY

The following cases are examples of progression in neurologic signs and symptoms in spite of vigorous and controlled liver therapy consisting of a pound of fresh liver or its equivalent daily over periods ranging from six months to two years. The case histories, briefly cited, indicate the nature of the signs and symptoms unaffected by the therapy and the new disabilities appearing during treatment.

CASE 20—A man, aged 67, was first seen on May 18, 1931, complaining of easy fatigue of one year's duration. He had some dizziness and dyspnea on exertion, but no neurologic complaints. Examination showed a red cell count of 2,600,000, 53 per cent hemoglobin and many macrocytes, hyperchromasia and a polymorphonuclear shift to the right in the smear. There was no free gastric acidity. Neurologic examination gave a negative result.

Course—The domestic liver extract first used by Castle and Bowie¹⁴ (prepared from 1 pound of beef liver) was administered daily. The blood count rose to 4,100,000 red cells per cubic centimeter, and the hemoglobin to 75 per cent and finally to 92 per cent. However, on Sept 26, 1932, the patient had marked numbness and tingling in the legs and marked disturbances in coordinate movements of the legs. The patellar jerks were exaggerated, the Romberg sign was positive, and sense of vibration was absent below the knees. Evidences of combined degeneration of the cord had developed while the patient was receiving adequate treatment with liver.

CASE 21—A man, 54 years of age, was first seen in June 1930 with the complaints of weakness, shortness of breath and numbness in the extremities of six months' duration. Examination showed a lemon-yellow color of the body, an atrophic tongue and achlorhydria. The blood count showed 1,050,000 red cells, 37 per cent hemoglobin, and anisocytosis, poikilocytosis, hyperchromasia and macrocytes in the smear. Neurologic examination showed active deep reflexes, a positive Romberg sign and loss of vibratory sense below the twelfth dorsal segment.

Course—In twenty-six days ventriculin brought the red cell count to 3,600,000 and the hemoglobin to 79 per cent. Later, both the red cell count and the hemoglobin were within normal limits. The equivalent of a pound of liver a day was used for two years and three months, but in spite of this, on Oct 14, 1932, there were found great spasticity in both legs, a bilateral Babinski sign and absent knee

¹⁴ Castle, W. B., and Bowie, M. A. A Domestic Liver Extract for Use in Pernicious Anemia, *J. A. M. A.* 92:1830 (June 1) 1929.

and ankle jerks, although the blood count and percentage of hemoglobin had remained normal. Serious progression had occurred under therapy.

CASE 22—A woman, aged 47, entered the clinic in January 1931 after having symptoms of fatigue for three years, heaviness in the legs, numbness, tingling and uncertainty of the position of the extremities. The red cell count was 4,080,000, the hemoglobin was 85 per cent, and in the blood smear macrocytes and a shift to the right were seen. There was no free gastric acidity. The patient had spastic paraplegia with exaggerated deep reflexes, positive Babinski and Romberg signs, a decreased sense of position in the legs and absent vibration sense below the twelfth dorsal segment.

Course—For two years the patient faithfully took domestic extract from 1 pound of liver a day and showed no improvement, but a slowly progressive increase in sensory symptoms. The sense of position became more grossly disturbed in both legs.

CASE 23—A woman, 51 years of age, entered the clinic on Oct. 17, 1930, stating that for six months she had noticed an increasing weakness and change in color. Examination showed a lemon-yellow color, an atrophic tongue, achlorhydria, a hemoglobin value of 87 per cent, and a red cell count of 4,360,000. There were macrocytes and a shift to the right in the blood smear. Neurologic examination showed exaggerated patellar and achilles jerks, a positive Babinski sign on the left and definite spasticity of the legs. Vibration was not felt below the twelfth dorsal segment and the sense of position was disturbed in the legs, so that the gait was that of spasticity plus ataxia.

Course—At first, six vials of liver extract and rest in bed for three weeks were prescribed, and then domestic extract of 1 pound of liver a day was taken continuously, with the exception of two months, for fifteen months. Yet on April 3, 1931, the patient's ataxia was increased, the feet were uncontrollable and she struck one ankle with the other on walking. Sewing was impossible. A constricting sensation appeared about the knees, and numbness increased. The exaggeration of deep reflexes was increased, and patellar and ankle clonus were elicited. Vibration was then absent below the seventh dorsal segment. On October 5, the Babinski sign was bilaterally positive and the symptoms referable to the lateral and posterior columns were worse.

CASE 24—A woman, 48 years of age, entered the clinic on Feb. 11, 1931, complaining of weakness of one year's duration (during which time Lilly's liver extract had been taken) and tingling and numbness in the feet and hands for three months, with some difficulty in walking. On entrance the red cell count was 3,200,000 and the hemoglobin 63 per cent. In the blood smear a shift to the right and macrocytosis were found. There was no free acid in the gastric contents, and the spleen was barely palpable. The deep reflexes were reduced and the ankle jerks absent. A positive Romberg sign was elicited, and vibratory sensation was absent below the fourth lumbar segment. The skin of the lower extremities was hyperesthetic.

Course—For three weeks from six to nine vials of Lilly's liver extract were taken daily, bringing the blood count to 5,000,000 and the hemoglobin to 90 per cent. Then a pound of liver was given each day in the form of domestic extract, so that at the time of this report the patient had been receiving adequate liver treatment for twenty-three months. In spite of this treatment, on Dec. 2, 1931, vibratory sense was decreased, the disability extending to the twelfth dorsal segment. Sense of position and coordination became affected, so that she could walk only with difficulty. On Oct. 24, 1932, the patellar reflexes were exaggerated, but the ankle jerks were still absent. Progression had occurred in the sensory sphere, and signs referable to the lateral tract had appeared.

CASE 25—A man, aged 60, had noted anorexia, dizziness and weakness for two months, associated with the sudden onset of burning of the tongue and a yellow skin. Examination on Nov 2, 1931, revealed no free gastric acidity, a red cell count of 1,580,000 and a hemoglobin content of 56 per cent. The deep reflexes were reduced, sense of vibration was diminished below the iliac crests, and the skin of the legs was hyperalgesic. Sense of position was impaired in the toes, and the Romberg sign was slightly positive. With the use of Lilly's liver extract, nine vials a day, the red cell count was brought up to 4,000,000 and the hemoglobin value to 85 per cent in fifteen days, and they remained at this level. One pound of domestic extract of liver was used each day for fourteen months. In spite of this, on June 10, 1932, the patient had greater difficulty in walking, the Romberg sign was grossly positive, and the vibratory defect had ascended to the level of the seventh dorsal segment.

CASE 26—A man, aged 43, entered the clinic on Aug 28, 1931, complaining of dyspnea, weakness, ease of fatigue, heavy sensations and numbness of the hands and feet, a sore tongue and impaired appetite for about six months. Examination showed an atrophic tongue, an enlarged spleen and pitting edema of the ankles. The red cell count was 2,200,000, and a smear showed anisocytosis, poikilocytosis, macrocytes and a shift to the right, the hemoglobin was 45 per cent. No free gastric hydrochloric acid was shown by the histamine test. The deep reflexes were all reduced, the Babinski response was negative. Sensation was normal except for reduced vibration sensibility in the lower part of the legs, and coordination was good.

Course—A good response was obtained with Lilly's liver extract, so that the red cell count was brought up to 4,400,000 and the hemoglobin to 84 per cent in two months, where they remained for the period of observation (fifteen months). Either domestic extract of 1 pound of liver or three vials of Lilly's liver extract were used daily. In spite of this, on April 8, 1932, the Babinski response was found to be bilaterally positive. Since then no change in the condition has appeared.

CASE 27—A woman, aged 44, was first seen in May 1930, at which time she gave a history of loss of appetite, weakness, tingling in the hands and feet, shortness of breath and a yellow color of fifteen months' duration. During this period liver therapy had been carried on under her physician's direction. Three weeks prior to admission the symptoms increased.

Examination revealed a pale yellowish skin, an atrophic tongue, an enlarged spleen and a rapid heart rate. The deep reflexes were equal and lively, the superficial reflexes, present. Sense of position and other sensory modalities were normal, and coordination was good. The Babinski responses were negative. Mental symptoms in the form of irritability and a decrease in memory were noted. The gastric contents contained no free hydrochloric acid, even with histamine. The red cell count was 1,500,000 and the hemoglobin 30 per cent, the leukocytes numbered 6,000 per cubic millimeter. Blood smears showed marked difference in the size and coloring of the red cells and a shift to the right.

Course—Four vials of ventriculin were given each day, with a reticulocyte response of 48.4 per cent on the seventh day. After three weeks the red cell count was 3,600,000 and the hemoglobin 70 per cent, later rising considerably more. The mental symptoms and paresthesia entirely disappeared, but the neurologic signs were unchanged. The dosage of ventriculin, four vials a day, was continued, but in February 1931, ten months later, reexamination showed an increase in neurologic signs. A bilaterally positive Babinski sign had appeared, and vibratory sense was reduced in the lower extremities. In spite of this the blood count, hemoglobin

and general strength remained normal. In December 1931, the patient returned, after neglecting her treatment for three months, with a relapse in the blood picture but no increase in neurologic signs. For the next twelve months she used the domestic extract of a pound of liver each day, with no change in her condition except the disappearance of paresthesia and a general feeling of renewed strength.

CASE 28—A man, 49 years of age, was admitted to Billings Hospital in September 1931, unable to walk. About six months previously he had begun to have a sense of dizziness, and finally had to give up work because of a feeling of insecurity. He was told that he had anemia, but was not treated until six weeks later when he went to a hospital, at which time he was given three vials of Lilly's liver extract a day. He improved and left the hospital after four weeks. After using liver extract, three vials a day for six weeks, the amount was reduced to two vials and then only one a day was taken. Six weeks previous to admission to Billings Hospital he began to have sensations of numbness and tingling over the hands and feet and lower part of the abdomen. This disappeared in a few weeks, and he began to notice a change in his gait, for it became increasingly difficult to walk.

During examination the patient was easily confused, he was unable to think of words, and his memory was poor. The tongue was bright red at the margins and atrophic. The liver and spleen were not palpable. There was redness of the left buttock with oozing from a few areas the size of a pinhead. There was moderate muscular weakness throughout. Spasticity was great and could not be overcome by force, there were ankle and patellar clonus. The Babinski sign was present bilaterally, the abdominal and cremasteric reflexes were absent. Very slight defense reflexes were present. There was a patchy preservation of the sense of pain in the legs, otherwise it was almost totally absent. Hypesthesia and hypalgesia were noted from the first lumbar to the fifth dorsal level, and there was hypesthesia of the hands and lower part of the forearms. Vibratory sense was absent below the eleventh dorsal vertebra. There were incoordination and loss of sense of position in the upper and lower extremities. The flow of urine was difficult to start.

The hemoglobin was 75 per cent, the red cell count 3,700,000, and the white cell count, 5,850. Smears showed anisocytosis and poikilocytosis with a few macrocytes, regeneration of the blood seemed active. There were polychromasia and an occasional nucleated red cell. The urine showed albumin with both white and red blood cells. The Wassermann and Kahn tests gave negative results in both the blood and the spinal fluid. The Ewald and histamine tests showed no free hydrochloric acid.

Course—After the obvious diagnosis of pernicious anemia with combined degeneration of the cord was made, a liver extract which was not a potent substance was given for nine days. There was an increase in the areas of redness over the buttocks, hips and heels. Symptoms increased in the bladder and edema was beginning on the lower extremities. Lilly's liver extract was administered first on Sept. 24, 1931. Six vials were given each day. In five days the reticulocyte peak was revealed at 11 per cent. Smears showed more macrocytes, and there was a more definite shift to the right. A septic temperature developed, and on September 29 an indwelling catheter was inserted. The hemoglobin was 60 per cent, the red cell count, 3,100,000, and the white cell count, 9,800. From this time on there was a progressive increase in all symptoms, probably owing to the infection. Edema of the legs was marked, and there was a reduction of plasma protein to 5.96 Gm per hundred cubic centimeters on October 19, 5.71 Gm on December 2.

and 669 Gm on December 11. There was a steady decrease in hemoglobin and in the red cell count on liver therapy. Decubitus ulcers sloughed increasingly, for which symptomatic treatment was given. The sensory loss extended upward to the second dorsal level. On December 12, the hemoglobin was 35 per cent, the red cell count, 2,000,000, and the white cell count, 21,000. Hypostatic pneumonia eventually developed, and the patient died on December 18, with no further change in objective neurologic findings.

Autopsy—There was acute suppurative pneumonia in the upper lobe of the right lung. In addition there were hemorrhagic cystitis and pyelitis with gangrenous urethritis and ulcerative involvement of the median lobe of the prostate. There was extensive gangrenous ulceration involving tissues about the sacrum and both trochanters, and perforating gangrenous ulcers were seen over both heels. There was a propagating thrombus in the right femoral and iliac vessels and the lower vena cava, distending and occluding them and extending upward into the vena cava and distally into numerous branches.

The peripheral nerves and nerve trunks showed no abnormalities. The brain contained a few areas of focal perivascular atrophy. The spinal cord was badly damaged throughout. The myelin sheaths were degenerated in the posterior and lateral columns and the periphery of the cord, but there were focal areas everywhere in the white matter in which the same process was apparent. The axons and glia were for the most part destroyed in the same areas, leaving a spongelike structure of vacuoles in a reticular network of sparse glia fibers. The recent lesions showed much fat in the vacuolated areas. There was no evidence of gliosis in the lesions.

CASE 29—A man, 26 years of age, was admitted to the hospital complaining of weakness, shortness of breath, palpitation on exertion and loss of appetite with nausea over a period of six months, finally forcing him to give up work. Examination showed a pale, weak, icteric person. The tongue was not atrophic. Over the base of the heart there was a systolic murmur believed to be hemic. The spleen was palpable, and the liver could be palpated at the costal margin. Although the patient felt weak, motor strength was not decreased. The blood tests showed hemoglobin, 25 per cent, red cells, 1,090,000, and white cells, 8,200. The blood smears revealed marked macrocytosis, anisocytosis and poikilocytosis. There was a definite shift to the right in the nuclei of the neutrophils, some of the cells showing as many as nine distinct lobes. The Wassermann and Kahn reactions were negative. No free hydrochloric acid was shown with the Ewald or histamine tests.

Course—The patient was given Lilly's liver extract no. 343 on Dec. 2, 1929, three vials a day. There was a 29 per cent reticulocyte count on the fifth day. He was discharged after eighteen days, with a hemoglobin value of 65 per cent and a red cell count of 3,800,000. He walked briskly and felt well, and his appetite was enormous. He was told to eat one-half pound of liver three times a week and to take two vials of liver extract a day. The patient made frequent returns to the outpatient department and was always in a depressed, melancholic or irritable mood. It is doubtful whether the prescribed liver was taken, although he was visited frequently by representatives of the social service department who provided the liver. The hemoglobin was rarely above 70 per cent, and the red cell count rarely was kept above 4,000,000 cells for more than a month at a time, but the neurologic status remained normal. In March 1931, the patient was studied for the first time in our special clinic. The deep reflexes were active and equal, and there was no clonus or Babinski sign. Abdominal reflexes were present. Coor-

dination and sense of position were normal, and there was no ataxia. Vibratory sense was decreased over the lower extremities. There were no objective or subjective sensory disturbances. The tongue was atrophic and the spleen palpable. The blood count at this time was 4,600,000 and the hemoglobin 92 per cent. The smears showed merely a shift to the right in the neutrophils. The patient was given six vials of liver extract a day for three weeks. Then three vials a day were ordered until April 1931. At that time it was decided to give the patient a domestic extract. His condition continued about the same, frequent neurologic examinations revealed no noteworthy change. In February 1932, there was an infection of the upper respiratory tract which reduced the hemoglobin to 45 per cent, the red cell count to 2,200,000 and the white cell count to 8,000, although liver had been taken as directed. At this time he was given 3 cc of Lederle's liver extract intramuscularly for eleven doses over a period of thirty-nine days. There was a prolonged low reticuloocyte response, and at the end of thirty-nine days the hemoglobin was 60 per cent and the red cell count 3,100,000. In May 1932, after taking 1 pound of liver a day in the form of a domestic liver extract, the hemoglobin was 82 per cent and the red cell count 4,140,000. Neurologic changes had occurred which were significant in the light of later findings. The knee and ankle jerks were not elicited, but there were no other abnormalities. It was decided to give the patient light work in the hospital, so that he could be watched more carefully. Intramuscular therapy with Lederle solution liver extract was again instituted. An injection of 3 cc was given five times in the next eleven days, and once a week thereafter, until the hemoglobin was 90 per cent and the red cell count 4,980,000. When examined on August 17, after he had been seen each week for some time, the patient reported that he had never felt so well, however, the knee jerks and ankle jerks were still absent, even with reinforcement. Although the patient felt better than he had for the past two years and had no subjective symptoms he had lost the knee and ankle jerks during a period when the blood was at a high level.

CASES WHICH SHOWED APPARENT IMPROVEMENT IN NEUROLOGIC STATUS

The following patients were kept on adequate liver therapy for long periods of time and showed what might be interpreted as improvement in some phases of the neurologic syndromes. Proper evaluation shows that the supposed improvement was in reality a progression of signs.

CASE 30—A white woman, aged 22, was seen for the first time on Jan 26, 1931. For two years, at frequent intervals, she had felt restless and nervous. In July 1929, she was cut on the right temple, right and left eyebrows and legs in an automobile accident. In two weeks she returned to work. Weakness of the legs and ankles then became evident. There was dull aching in the feet, with some puffiness which was relieved by rest. In November 1929, constipation was marked, and there was bright red blood in the stool, so that a diagnosis of hemorrhoids was made. In the year previous to our first observation there was some disturbance in the sensation of the legs, for the patient felt as if she were walking on "felt." Numbness and tingling were noted together with weakness in the ankles and legs. There had been a loss of 15 pounds (6.8 Kg.), with considerable loss of strength in the last few years.

The pupils reacted to light and in accommodation. The liver and spleen were not palpable, and the tongue was not atrophic. The upper reflexes were hyper-

active and the abdominal reflexes present, but knee and ankle jerks were absent. The Babinski and Romberg responses were both negative. Sense of position and coordination were disturbed in the lower extremities. Vibratory sense was markedly diminished below the tenth dorsal segment and tactile discrimination and sensation were impaired over an area between the knee and the midcalf bilaterally. This examination was checked by several members of the neurologic department.

The Wassermann and Kahn reactions of the blood were negative on two occasions, and the spinal fluid also gave negative reactions to these tests. The urine was normal. There was no free hydrochloric acid according to the Ewald and histamine tests. The hemoglobin was 85 per cent and the red cell count 4,300,000, smears showed none of the typical changes of pernicious anemia except slight hyperchromasia and a few toxic neutrophils.

Course—A diagnosis of pernicious anemia with degeneration of the posterior column without anemia was made. The patient was ordered to take 1 pound of domestic liver extract a day. She was seen several times in the next three months, and showed no change in neurologic findings except in the development of hyperalgesia over the lower extremities from the knees down. When she was next seen, in April 1932, four months after the first visit, the patellar jerks had returned and were markedly active. All other findings were as before, including the change in deep sensation. This, then, is a definite case of progression in the lateral column, and will be discussed later in the paper. The blood continued to be normal. The patient felt better subjectively and had no complaints.

CASE 31—A woman, aged 70, was first seen by us on Sept 9, 1931, with the story of two years of ill health, the condition having been diagnosed as pernicious anemia, during this time irregular and insufficient treatment with liver had been given. The disease had begun with tingling and numbness of the hands and feet, but during the past year she had had marked uncertainty in walking and had fallen several times. The patient noted a marked generalized progressive weakness. The red cell count was 3,500,000 and the hemoglobin 78 per cent. According to the histamine test there was no free acid in the gastric contents. Neurologic examination revealed marked impairment of the sense of position in the lower extremities below the knees. The deep reflexes were all reduced and the achilles jerks absent. The Babinski sign was negative, the Romberg sign, positive.

Course—After taking domestic liver extract, 1 pound a day, the patient became stronger, the red cell count rose to 4,500,000 and the hemoglobin to 89 per cent. In spite of this improvement the defect in vibratory sense ascended to the fifth dorsal level, and spasticity appeared in the lower extremities.

CASE 32—A man, aged 45, entered the clinic on Feb 13, 1931, complaining of weakness and numbness and tingling in the legs of one year's duration. In the last four months fatigability had become progressive, and he found himself stumbling when walking in the dark. Hyperalgesia of the finger-tips developed. For eight months he had been given arsphenamine intravenously on the assumption that the condition was tabes dorsalis.

Neurologic examination revealed slightly irregular pupils which responded well to light and in accommodation. General muscular strength was diffusely decreased. The gait was spastic, and tone in the lower extremities was increased. The knee jerks were exaggerated and the ankle jerks absent, a bilateral positive Babinski sign was obtained. The Romberg sign was positive, and coordinate movements of the lower extremities were badly performed. Hypalgesia was noted in the lower extremities from the knees down, sense of position was poor in the legs,

and vibratory sensibility was diminished or absent below the level of the tenth dorsal segment. The superficial reflexes were present and lively. The tongue was smooth at the edges, but no other somatic sign could be found. Gastric analysis showed no free hydrochloric acid even after the injection of histamine. The red cell count was 4,500,000 and the hemoglobin 87 per cent. There was a shift of the neutrophils to the right, with anisocytosis. The Wassermann and Kahn reactions were negative in both the blood and the spinal fluid on several occasions.

Course—The patient was given treatment for pernicious anemia, consisting of domestic extract from 1 pound of liver a day. The tired feeling and ease of fatigue rapidly improved, and the numbness and tingling gradually decreased. In July 1931, an attack of pyelitis with a febrile reaction brought the red cell count down to 3,900,000 and the hemoglobin to 72 per cent, but the blood smears showed little change. Aside from this period the patient's strength remained good, allowing him to return to work, the blood count and hemoglobin remained normal. In spite of improvement in the general condition no change in the objective neurologic findings was noted during the two years of observation, although persistent adequate liver therapy has been maintained.

CASE 33—A man, aged 58, had general loss of strength, tingling of the fingers and toes and intermittent attacks of yellow coloration of the skin for three years. In the autumn of 1929 he was compelled to give up work, but the correct diagnosis of pernicious anemia was not made until January 1930, after which he was given two blood transfusions and insufficient liver therapy. In September 1931, an unsteady gait developed, and in October mental symptoms appeared in the form of disorientation and confusion. On admission to Billings Hospital on Jan 11, 1932, he was disoriented and at times irrational. His memory for recent events was poor, but for past events good, and his statements concerning the history were reliable.

Neurologic examination revealed a fine vertical nystagmus and slightly diminished sensibility to pin-prick on the right side. The deep reflexes were all lively and the abdominal reflexes absent. There were a bilateral unsustained ankle clonus and a bilateral Babinski response. Coordination and sense of position were poor in all the extremities, and there was a marked coarse ataxia of the arms and legs. There was a marked generalized asthenia, so that the patient could hardly stand or support his extremities against gravity. The result was that all movements were performed with wide oscillations in range.

The spleen was just palpable. The red cell count was 2,400,000 and the hemoglobin, 50 per cent. There were hyperchromasia and many macrocytes from 13 to 14.8 microns in diameter. Anisocytosis and poikilocytosis were noted, as well as a shift of the neutrophils to the right. Even after the injection of histamine there was no free acid in the gastric contents.

Course—Three vials of Lilly's liver extract no. 343 were given three times a day, causing a reticulocyte rise to a peak of 11 per cent on the twelfth day. The rise in red cells and hemoglobin was slow, so that three doses of Lilly's solution liver extract were administered intramuscularly. On February 1, the patient became more oriented (the red cell count was 3,400,000 and the hemoglobin 66 per cent). On February 5, the patient was well oriented, the red cell count was 3,800,000 and the hemoglobin was 68 per cent. At this time the patient's strength had so improved that his movements became steadier and smoother, but the finger-to-nose and heel-to-knee tests still showed some ataxia. The Babinski responses and the Romberg sign were positive. The clonus and sensory findings were as before. On April 18, with the red cell count 4,700,000 and the hemoglobin

105 per cent, the sense of position of the legs was evidently more disturbed. The patient walked on a wide base, and the Romberg sign was positive. The gait then was definitely spastic, and the reflexes were markedly exaggerated. On May 15 the red cell count was 4,600,000 and the hemoglobin 104 per cent. The gait was more spastic and the deep reflexes were more exaggerated. This state continued, with the red cell count well over 4,500,000 and the hemoglobin over 100 per cent. During the year of observation the patient consumed the domestic extract of 1 pound of liver each day.

COMMENT

In this patient, with severe symptoms for at least three years, inadequately treated, there developed profound mental and neurologic symptoms engrafted on severe weakness. The mental symptoms quickly disappeared on rejuvenation of the blood, the weakness cleared less rapidly. When strength returned, the striking motor disability disappeared, but the neurologic symptoms and signs remained, in fact, spasticity progressed during a year of adequate therapy. Although the patient now walks and moves well, as contrasted with a previous bedridden state, degeneration of the cord has progressed. This is a striking example of a possible false interpretation of the effect of change in general bodily strength on the neuromuscular status of the patient after therapy.

CASES SHOWING DEFINITE SIGNS OF IMPROVEMENT

CASE 34—A white woman, 74 years of age, was admitted to the University of Chicago Clinics on Nov. 25, 1929, complaining of a tingling sensation in her hands for several months. Her tongue was sore, and there was a peculiar prickly sensation extending up the spine to the scalp. There was marked irritability. For ten years the patient had had diabetes mellitus, easily controlled by diet.

Examination showed a well nourished woman, pale but not acutely ill. There was loss of vibratory sense from the iliac crests downward with the exception of the right knee joint. The ankle jerks were absent on both sides. The right knee jerk was absent and the left very sluggish. The Babinski reflex was negative, and the abdominal reflexes were absent. There was no definite ataxia. The motor strength was fair. Examination of the blood showed red cells, 1,900,000, white cells, 3,400, hemoglobin, 48 per cent. Blood platelets were decreased. There were macrocytes present, and the cells showed hyperchromasia. There was a shift of the neutrophils to the right. The Ewald and histamine tests showed no free hydrochloric acid.

Course—Treatment with Lilly's liver extract was started on Dec. 13, 1929, with four vials a day for three days and then six vials a day, producing a reticulocyte rise of 15.5 per cent on the sixth day. On Jan. 15, 1930, the hemoglobin was 73 per cent and the red cell count 4,100,000, or double that of ten days previously. The patient felt improved subjectively, walked about alertly and was less irritable. She was discharged, with orders to take two vials of liver extract a day. From time to time she was seen, both for treatment of the diabetes mellitus and for a check of the neurologic findings. On Sept. 2, 1932, the hemoglobin was 100 per cent and the red cell count 4,980,000. The reflexes of the upper extremities were active. However, the knee jerks and ankle jerks were absent. On November 7, the blood level was still high. The gait was slightly ataxic, but the upper

extremities were coordinate. The right triceps jerk was reduced, the left was present, and the lower deep reflexes were all absent except the right knee jerk, which was lively, whereas before it had been absent. There was no Babinski reflex or ankle clonus. Sense of vibration was diminished from the iliac crests, but other sensations were normal. Subjectively the patient was feeling very well for her years. Improvement had occurred only in the mental symptoms and peripheral dysesthesia.

CASE 35—An uncooperative man, aged 56, was first seen on Feb. 12, 1930, after symptoms of from five to six years' duration, during the latter part of this period he had used liver extract irregularly. Neurologically the patient showed decreased knee jerks, absent ankle jerks, a positive Romberg sign and absence of vibratory sense in the legs. He was agitated, had many delusions and was with difficulty prevented from wandering about the ward at all times. On February 20, the red cell count was 800,000 and the hemoglobin 40 per cent. On March 17, he became normal mentally, and the blood picture showed 3,300,000 red cells and 60 per cent hemoglobin.

He was difficult to treat and refused to take the liver regularly. The neurologic symptoms increased, absent knee jerks, exaggerated upper deep reflexes and ataxia were noted, and the positive Romberg sign became worse. On Sept. 1, 1931, he was brought into the hospital again in an irrational state with a red cell count of 1,100,000 and 34 per cent hemoglobin. On September 21, he was rational again, with a red cell count of 3,500,000 and 60 per cent hemoglobin. During the subsequent fifteen months on adequate liver therapy the blood remained normal, but the neurologic defects continued to progress slowly. The irrational episodes were correlated with marked anemia and were alleviated by raising the blood count.

CASE 36—The patient, a man, aged 62, was first seen on Sept. 20, 1930, with weakness in the legs and knees for six weeks. He had marked numbness and tingling of the toes and fingers. At that time the red cell count was 1,600,000 and the hemoglobin was 49 per cent. There was no free gastric acidity and the tongue was sore. There were slight changes in vibratory sensation in the legs, but no other neurologic findings. With nine vials of Lilly's liver extract a day a reticulocyte response of 23 per cent was obtained on the tenth day. On Nov. 12, 1930, the red cell count was 4,690,000 and the hemoglobin was 92 per cent. On December 9 the red cell count had changed to 5,250,000 and the hemoglobin to 101 per cent. At this time the numbness and tingling disappeared and have remained absent as the blood count has remained up.

CASE 37—A man, 45 years of age, was admitted to the clinic on Sept. 1, 1932, complaining of a tired feeling and numbness and tingling of the hands and feet over a period of one year. He had been nervous and irritable over the same length of time. In October 1930 the numbness and tingling had spread up the arms to the elbow. Two months later numbness was progressive up to the knees and associated with a stiffness of both upper extremities. He began to feel unsteady on his feet and was never sure that his feet were in contact with the ground.

There were no abnormal physical findings except those of the nervous system. The patient walked on a wide base and was slightly unsteady. There was spasticity of the lower extremities, and the knee jerks and ankle jerks were exaggerated. The Romberg response was positive. Sense of position and coordination were normal and vibratory sense was only slightly reduced. The Babinski reflex was negative. The hemoglobin was 90 per cent and the red cell count 5,010,000. The smears looked normal. There was no free hydrochloric acid according to the Ewald or histamine tests. The Wassermann reactions of the blood and spinal fluid were negative.

Course—A diagnosis of pernicious anemia was made, and the patient was told to take liver extract from 1 pound of liver daily. Subjectively the patient felt improved. There was still paresthesia in the hands and feet. On the next visit, three months later, neurologic findings were the same, but the patient was feeling so well that he wished to discontinue the liver therapy for the summer. The importance of liver therapy was explained, but he wished a rest. Two months later he returned because he was not feeling well. The symptoms were vague, he tired easily and felt fatigued most of the time. Neurologic findings were as before. The blood was still normal.

This patient, without anemia or a suspicious blood picture, showed evidence of combined degeneration of the cord. Subjective improvement occurred on treatment with domestic liver extract from 1 pound of liver a day. A period of two months without therapy caused a return of the tired feeling and fatigability. Objective neurologic tests remained the same.

COMMENT

A study of case histories is not an adequate method of evaluating a form of treatment, especially when the signs and symptoms which may undergo improvement require considerable skill to elicit. The comparison of findings brought out by one examiner before therapy and another after therapy offers obvious objections, the patient should be observed throughout the period of treatment by the same examiner. In many cases remarkable improvement was reported because of the multiplicity of examiners, furthermore, in the available literature not one neurologist has reported improvement in his cases. In all the cases herein reported the patients were reexamined by us at frequent intervals over a variable but usually adequate total period of time, and assurance was at hand that ambulatory patients were fulfilling therapeutic suggestions.

Weakness is an important symptom of pernicious anemia, depending in degree on the severity of the anemia. Case 37 is a possible exception, since the weakness was unassociated with anemia and was directly improved by liver therapy. However, weakness usually rapidly and often completely recedes when the blood count is brought up to figures approaching normal, and therefore is amenable to liver therapy. Weakness often produces effects which resemble the results of primary damage to the central nervous system. A weak person is ataxic and incoordinate, in fact, with a severe anemia his gait is often worse than that seen in advanced tabes dorsalis or cerebellar disease, he may be unable to walk at all. The muscles become flabby and hypotonic, and the deep reflexes may be markedly decreased. During treatment, as the blood count rises, the strength improves, and simultaneously the supposed neurologic signs and symptoms rapidly regress in a period of time much too short for any anatomic regeneration or physiologic reorganization. Case 33 is

such an example. The rapidity of effect resembles that seen after feeding a depleted animal a single dose of vitamin B₂. Furthermore, as strength increases the patient is able to compensate by voluntary effort for mild defects in his sense of position or changes in muscle tone. Careful examination will show no actual change in objective neurologic signs.

Before evaluating the effects of liver therapy on the spinal cord complications of pernicious anemia, it is necessary to know what clinical changes might be expected from improvement. The terms posterolateral sclerosis and combined degeneration of the cord are indicative of the seat of greatest damage to the spinal cord—the posterior and lateral (particularly posterolateral, wherein lies the pyramidal system) tracts. Other regions of the cord are involved to a less degree. Lesions of the posterior regions of the cord will cause decrease in tone and deep reflexes and disturbance of coordination and position sense. Lesions of the lateral regions will effect an increase in tone and in the deep reflexes, a positive Babinski reflex and changes in sensation referable to damage of the long spinothalamic tracts, while troubles in coordination will be masked by the spasticity.

It can easily be seen that the effects of the involvement of the posterior and lateral columns on muscle tone and deep reflexes are opposite in character. Combinations occur which vary in each case. Assuming that posterior column signs of decreased tone and decreased reflexes could improve, the evidence would be a return of tone and reflex activity to their normal intensity. However, supposing that the posterior column symptoms were unaffected by treatment, but progression occurred so that the lateral tracts became involved, tone and reflex activity would return to normal or become exaggerated. If lateral tract symptoms of hyperreflexia and hypertonia were to improve, the result would be a decrease in those signs exactly as if added damage were to be inflicted on the posterior horns and columns. The syndrome of combined degeneration of the cord is a combination of degeneration of the lateral and the posterior columns, hardly ever quantitatively equal, but varying in degree in each case and frequently associated with successive rather than simultaneous initial involvement. Thus, great errors may be introduced in the evaluation of neurologic signs, mistaking progression of the disease for its improvement. However, the Babinski response on the one hand and the character of the sensory changes on the other will serve to indicate the true state of affairs. If tone and reflexes were to return in a person who had a posterior cord lesion his sense of position and vibratory sensibility should also return (case 30), while in involvement of the lateral tract losses of pain and temperature sense should recede.

In this series of cases we were unable to discover, even in patients who ingested a pound of liver a day for two years any improvement

in the organic neurologic signs or symptoms (cases 1 to 19, table) Once the rapid improvement in strength was discounted, and if care were observed to avoid falling into the error of interpreting progression as regression, one can apply the same statement to most of the cases reported in the literature This result is not at all surprising to one familiar with the pathologic findings of combined degeneration of the cord The entire neuron is destroyed in small foci, often in perivascular areas throughout the cord, but most markedly in the posterior and posterolateral columns There is no selective demyelination, but the whole structure is destroyed, including most of the glial stroma Astrocytic invasion of the damaged area is minimal, so that a status spongiosus is formed The possibility of such a lesion undergoing improvement is unthinkable, unless, as Suzman and Ungley have suggested, regeneration of central nerve fibers could occur Gerard and Grinker¹⁵ have shown that even in immature mammals under ideal circumstances regeneration cannot take place Furthermore, Davidson, on examination of several adequately treated patients with combined degeneration of the cord found no neuronal regeneration, but a proliferation of glia seemed to have been stimulated, causing a glial scar to form in an otherwise spongy tissue

Collier stated that he had never seen complications referable to the spinal cord develop in a case of pernicious anemia after it had come under observation, and Piney recently reiterated this opinion They meant that once the anemia has developed, degeneration of the cord either is obvious at the onset or never develops This statement is somewhat extreme, although one of us (R. R. G.¹⁶) found that when the clinical disease includes nervous complaints in the original list of symptoms, degeneration of the cord will develop about four times more frequently than in those cases in which nervous complaints develop after the onset Numerous exceptions to this statement are constantly encountered, and it is known today that there exists no constant relationship between the degree of anemia and the degeneration of the cord It is likely that as liver therapy prolongs the lives of patients with pernicious anemia, the number of cases of degeneration of the cord will increase

Notwithstanding the impossibility of improving cord symptoms, liver therapy would be of great advantage if further damage could be prevented or if onset of involvement of the cord could be prevented Such a prophylactic action of liver cannot be concluded, as Starr did from a series of 4 cases In our series of cases progression of symptoms and

15 Gerard, R., and Grinker, R. R. Regenerative Possibilities of the Central Nervous System, *Arch Neurol & Psychiat* **26** 469 (Sept) 1931

16 Grinker, R. R. Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship, *Arch Int Med* **38** 292 (Sept) 1926

signs in the cord occurred in patients under continuous and adequate liver therapy, with blood counts within normal limits (cases 20 to 29). In our cases progression was not more noteworthy in insufficiently treated patients than in those receiving adequate therapy over a long period of time. The factors concerned in progression, like those involved in the etiology of the degeneration of the cord, are not related to the liver intake or to the height of the blood count. Our experience shows that cord symptoms develop rather suddenly and come to a certain maximum rapidly, and then either remain stationary for a long period or slowly progress, no matter what is done for them.

Patients in whom cord symptoms develop before any sign of blood dyscrasia are numerous enough to offer difficulties in diagnosis. Two such cases (30 and 32) are included in this series, and several others have been seen. They show achlorhydria and signs of dorsal, lateral or combined column degeneration. Vague signs are often present in the blood in the form of a shift in the Price-Jones curve or neutrophils of pernicious anemia, but often it is several years before true anemia develops. The public acceptance of the dictum that liver prevents anemia may be responsible for an increasing number of these cases. With liver forming a part of the diet of large groups of the population, neurologic diagnosis of the cause of degeneration of the cord must depend less and less on the presence of anemia and more on the character of the changes in the cord, the achlorhydria and the blood smear.

A further difficulty lies in the differentiation between permanent cord symptoms and peripheral nerve symptoms, from which the patient will recover. The criteria used to separate these two neurologic complications of pernicious anemia are not definite. Using dysesthesia as evidence of damage to the cord, Woltman found that combined degeneration developed in 80 per cent of cases of pernicious anemia. Using other criteria, one of us (R. R. G.) found that only 30 per cent showed this complication. As Hamilton and Nixon have shown, degeneration of the peripheral nerves is not infrequent in pernicious anemia. The usual clinical picture is that of dysesthesia with some hyperalgesia. The skin may become atrophied, smooth and shiny. In more advanced cases objective sensory losses and actual atrophies may appear. The process attacks the distal portions of the extremities, especially the hands. It has a definite relationship to the degree of anemia and is probably due, like the homologous change in peripheral arteriosclerosis, to an anoxemia of the distal nerve fibers. Improvement gradually occurs when the anemia regresses, since peripheral nerve fibers regenerate with ease. Rapidly disappearing dysesthesia is probably due to a functional disturbance before actual degenerative changes have appeared. It is, of course, a question whether disturbances in deep sensation may not be selective according to involvement of the peripheral nerves, as in the

example of postdiphtheritic neuritis of the ataxic type. Some of the rapid sensory restitution reported after liver therapy, if a true finding, may indicate the origin of the disturbances in the peripheral nerves.

Mental symptoms may well be due to focal areas of destruction in the brain, the well known Lichtheim plaques. More often the disorientation and irrational state are due to the anemia alone. Case 35 demonstrated two episodes of severe anemia in the same patient accompanied by mental symptoms. These conditions change quickly when the red cell count approaches 3,000,000. The effect of therapy alone serves to differentiate the organic changes from those due to the anemia.

CONCLUSIONS

1. Liver therapy is not efficacious in improving or preventing degeneration in the central nervous system complicating pernicious anemia.

2. Liver improves the general strength of the patient with combined degeneration of the cord by increasing the number of red cells in the circulating blood or by some obscure direct action. Weakness may closely imitate the effects of damage to the spinal cord.

3. Liver cures the mental symptoms of pernicious anemia, which are usually caused by the anemia.

4. The peripheral nerve complications of this disease, consisting of dysesthesia, atrophic changes in the skin and perhaps other dissociated sensory defects, are alleviated by the recession of the anemia. Such complications are much more frequent than they are usually believed to be.

5. The majority of cases of combined degeneration of the cord develop rapidly at the onset and then progress slowly, no matter what therapy is employed. Gradual progression of signs may be falsely interpreted as signifying improvement.

6. Combined degeneration of the cord develops not infrequently before the anemia and should be diagnosed by the character of the cord syndrome, the achlorhydria, glossitis and blood smear.

7. Liver therapy in pernicious anemia should be controlled by the height of the blood count. Quantities of liver in excess of that necessary to maintain a normal blood level are wasted.

NOTE.—The patients described in this report have been given Lederle solution liver extract intramuscularly since March, 1933, and are being watched for neurologic changes.

CHARACTERISTICS OF THE SYNOVIAL FLUID IN VARIOUS TYPES OF ARTHRITIS

STUDY OF NINETY CASES

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The etiologic diagnosis of arthritis frequently presents many difficulties, and in many cases the cause remains obscure. For that reason, every effort should be made to obtain as much information as possible from the study of the course of the disease and the characteristics of the synovial fluid. During the past two years, we have studied a hundred and twenty samples of synovial fluids from ninety patients with various types of arthritis. We were interested in determining what information of diagnostic value could be obtained from the study of synovial fluid. The types of cases studied are listed in table 1.

METHODS

All the patients were studied while residing in the hospital. With a needle and syringe, fluid was aspirated from the joints, the usual aseptic precautions being taken. The skin was anesthetized with a 2 per cent solution of procaine hydrochloride.

A sample of the aspirated fluid was mixed with sodium oxalate crystals to prevent clotting and examined chemically for the content of total protein, sugar and nonprotein nitrogen. In forty-five cases, blood was withdrawn from a vein simultaneously for comparison of the sugar and nonprotein nitrogen content of the blood and the synovial fluid.

Aspiration was not performed following a period of fasting, so that this factor will require consideration in the interpretation of the comparative results, to be discussed presently.

Total cell counts were done on the synovial fluid immediately after aspiration. Differential cell counts were done according to the supravital technique. Gonococcic complement fixation tests were done on the blood and synovial fluid in a number of cases, and the Wassermann test was likewise done on both the blood and the synovial fluid.

The synovial fluids were cultured for micro-organisms, and in suspected cases of tuberculous arthritis samples of the fluid were injected into guinea-pigs.

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OBSERVATIONS

Gonococcic Arthritis—In another place we¹ have presented the results of a study of the synovial fluid in gonococcic arthritis, and we include a summary of the findings in this article in order that they may serve as a basis for comparison with other types of arthritis. To repeat briefly, it was found that the synovial fluids from cases of gonococcic arthritis could be divided into two groups, on a basis of the presence or absence of organisms. The results of the study have been included in table 10. On the whole, the average cell count was higher in the infected fluids. The polymorphonuclear leukocytes were more abundant, and the other cells were fewer in number in the infected fluid than in the non-infected samples. The total protein content was increased above the

TABLE 1—Types of Cases Studied

	Number of Cases	Number of Specimens of Synovial Fluids Examined
Gonococcic arthritis	41	53
Rheumatic fever	15	19
Rheumatoid arthritis	16	22
Tuberculous arthritis	5	10
Miscellaneous cases	13	16
Chorea joints	3	
Syphilitic arthritis	2	
Scurvy	1	
Hemolytic streptococcal arthritis	3	
Traumatic arthritis	2	
Myocardial insufficiency	1	
Degenerative arthritis	1	
Total	90	120

normal in both, the nonprotein nitrogen value was the same as that of the blood, and the sugar content varied in three factors: the number of leukocytes in the synovial fluid, the presence of micro-organisms, and the level in the blood at the time, or before, aspiration of the joints. The gonococcic complement fixation test was positive in 86 per cent of the cases in the blood and in 76 per cent of the cases in the synovial fluid. Usually the results of the tests in the synovial fluid and the blood were in agreement. Rarely, the blood serum showed a positive reaction before the synovial fluid.

Acute Rheumatic Fever—The synovial fluids from fifteen patients with rheumatic fever were studied. Total and differential cell counts

1 (a) Myers, Walter K., and Keefer, Chester S. The Gonococcal Complement Fixation Test in the Blood and Synovial Fluid of Patients with Arthritis, *New England J. Med.* **211** 101, 1934. (b) Myers, W. K., Keefer, C. S., and Holmes, W. F., Jr. The Characteristics of Synovial Fluid in Gonococcal Arthritis, *J. Clin. Investigation* **13** 767, 1934.

were done on nineteen samples of fluid, and the results are recorded in table 2 and summarized in table 10. In all cases, the polymorphonuclear cells predominated, and, as a rule, the higher the total count the greater the relative number of polymorphonuclears. As a rule, the monocytes and clasmotocytes were present in larger numbers in the cases with low total counts. All the fluids were sterile on bacteriologic culture. The results of the chemical examinations of twelve samples of synovial fluid are recorded in table 3 and summarized in table 10. The non-protein nitrogen value was practically the same as in the blood, whereas the sugar content of the synovial fluid was the same as or higher than

TABLE 2—Total and Differential Cell Counts of Synovial Fluid in Rheumatic Fever

Case Number	Total Cell Count, per C Mm	Differential Cell Count, per Cent				
		Polymorpho nuclears	Lympho cytes	Monocytes	Clasmato cytes	Eosino phils
41	8,850	70		11	19	
42	13,500	8	4	3	10	
43	4,250	75	3	6	18	
46	2,150 R *	89	2	2	7	
	10,450 I	88	7	2	3	
52	39,500	97			3	
53	2,900 R	97	1		2	
	3,200 I	78	2	6	14	
54	26,600	95		5		
55	3,550	86	1	7	6	
56	12,550	95		4	1	
58	34,350	92	3	5		
59	16,850	78	3	11	8	
60	21,800	96	2	2		
61	22,000	97	2	1		
62	21,500 I	89	7	3	1	
	15,000 R	92	1	4	3	
63	11,500 R	91			9	
	15,450 L	98			2	

* R indicates that the data are on the right knee and L on the left knee

that of the blood. This is evidence of a noninfected fluid. The higher values in the synovial fluid can be explained on the basis of the fact that most of the examinations were done several hours after a meal, and it is known from previous work² that the fall of the sugar content of the blood precedes that of the synovial fluid.

Rheumatoid Arthritis—Twenty-three fluids from sixteen patients were studied. The results of the cell counts are recorded in table 4 and summarized in table 10. In most cases the polymorphonuclear cells predominated, but the variations in the number of different cells were wide. This probably depended to some extent on the type of cellular reaction in the synovial cavities at the time of aspiration. All the fluids

2 (a) Cajori, F. A., Crouter, C. Y., and Pemberton, R. The Physiology of Synovial Fluid, Arch Int Med 37:92 (Jan) 1926. (b) Allison, N., Fremont-Smith, F., Dailey, M. E., and Kennard, M. A. Comparative Studies Between Synovial Fluid and Plasma, J Bone & Joint Surg 8:758, 1926.

TABLE 3—Results of Chemical Examination of Blood and Synovial Fluid in Rheumatic Fever

Case Number	Total Protein in Joint Fluid, Gm per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc		Sugar, Mg per 100 Cc		Cells, per C Mm
		Blood Plasma	Joint Fluid	Blood	Joint Fluid	
44	2.0	26	28	71	74	13,500
45	2.3	37	33	87	125	4,250
47	3.8	35	35	108	121	2,450
52	3.6	32	30	115	130	39,500
53	3.4	25	22	116	146	2,900
	3.4	25	26	116	155	3,200
54	3.0	27	22	79	109	26,600
55	4.3	20	19	90	109	3,550
56	4.6	32	33	143	155	12,550
58	4.7	35	35	123	104	34,350
59	4.1	35	32	84	84	16,850
63	3.9	24	24	78	91	11,500

TABLE 4—Total and Differential Cell Counts in Synovial Fluid of Patients with Rheumatoid Arthritis

Case Number	Total Cell Count, per C Mm	Differential Cell Count, per Cent				
		Polymorpho nuclears	Lympho cytes	Monoocytes	Clasmato cytes	Eosino phils
42	9,875	91	1	4	3	
45	1,600	84	9	6	1	
50	20,100	91	5	4		
51	17,400	94	5	1		
	16,900	100				
75	6,650	3	67	26	4	1
80	14,600	72	19	7	1	1
81	3,400	60	21	2	2	15
82	67,400	21	22	10	57	
	74,800	16	5	14	65	
83	43,300	84	6	8		2
84	23,200	98	2			
85	1,700	26	26	16	32	
86	39,800	95	1	2	2	
	28,000	85	6	9		
	25,650	87	8	3	4	
87	25,400	84	7	2	7	
	24,350	98	1		1	
88	14,150	77	16	6	1	
	11,900	85	13	1	1	
	12,650	85	12	2	1	
89	12,000	91	4	5		
90	38,700	97	3			

TABLE 5—Results of Chemical Examination of Blood and Synovial Fluid in Rheumatoid Arthritis

Case Number	Total Protein in Joint Fluid, Gm per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc		Sugar, Mg per 100 Cc		Cells, per C Mm
		Blood Plasma	Joint Fluid	Blood	Joint Fluid	
42	3.8	29	28	129	125	9,875
46	3.7	26	21	85	99	1,600
51	2.4	35	46	76	80	17,400
75	4.2	50	33	77	94	6,650
80	6.1		20	74	78	14,600
81	4.5	29	29	101	124	3,400
87	4.8	33	23	52	100	25,400
88	5.1	26	20	89	91	14,150
90	2.3	26	24	111	87	38,700

were sterile. Chemical examinations of the blood and synovial fluid for the nonprotein nitrogen and sugar content, as well as the total protein content of the synovial fluid, were made of nine samples. The results are recorded in table 5 and summarized in table 10. The total protein values varied from 2.3 to 6.1 Gm per hundred cubic centimeters, the nonprotein nitrogen value was essentially the same in the synovial fluid as in the blood, and the results of the examination for the sugar content were either the same as those in the blood or somewhat higher.

TABLE 6—*Total and Differential Cell Counts of Synovial Fluid in Tuberculous Arthritis*

Case Number	Total Cell Count, per C Mm	Differential Cell Count, per Cent				
		Polymorpho nuclears	Lymphocytes	Monocytes	Clasmato cytes	Eosinophils
66	110,000	79	3	11	7	
76	45,200	89	7	1	1	2
77	13,450	9		2	5	
78	11,600	52	30	16	1	1
79	6,500	45	26	26		3
	12,080	75	16	5	4	
	13,100	61	18	17	4	
	13,400	93	4	2	1	
	13,000	56	12	31	1	
	13,970	86	7	2	5	

TABLE 7—*Results of Chemical Examination of Blood and Synovial Fluid in Tuberculous Arthritis*

Case Number	Total Protein in Joint Fluid, Gm per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc		Sugar, Mg per 100 Cc		Cells, per C Mm
		Blood Plasma	Joint Fluid	Blood	Joint Fluid	
77	5.5	21	16	102	116	13,450
78	4.3	28	22	74	79	11,600
79	4.6	22	18	102	160	6,500
	4.7	20	22	79	91	13,980
				80	93	13,400

Tuberculous Arthritis—Synovial fluids from five cases of tuberculous arthritis, proved by the inoculation of guinea-pigs, were studied. The results of the total and differential cell counts are recorded in table 6. The results of the chemical examinations of four samples are recorded in table 7 and summarized in table 10. The total cell counts were between 6,500 and 110,000 per cubic millimeter, and while the differential formula showed no absolutely characteristic features, it was somewhat more common to observe greater numbers of lymphocytes and monocytes than in the other types of arthritis. The chemical examinations revealed nothing strikingly characteristic.

Miscellaneous Types of Arthritis—The results of the total and differential cell counts of sixteen samples of synovial fluid from thirteen

patients with various disorders of the joints are summarized in table 8. The chemical examinations in four cases are included in tables 9 and 10.

Total Protein of Synovial Fluid—The values for total protein included the mucin, as it was not removed by precipitation before the determinations were made. In all cases, the total protein value was

TABLE 8—*Total and Differential Cell Counts of Synovial Fluid in Miscellaneous Cases of Arthritis*

Case Number	Diagnosis	Total Cell Count, per C Mm	Differential Cell Count, per Cent			
			Polymorpho nuclears	Lympho cytes	Mono cytes	Plasmat ocytes
47	Traumatic arthritis	4,800	94	3		3
48	Charcot's joint	160	42	6	12	40
		140	70	10	20	
49	Hemolytic streptococcal arthritis	109,500	100			
64	Hemolytic streptococcal arthritis	350,000	96	1	1	2
65	Hemolytic streptococcal arthritis	251,000	94	1		5
67	Congenital syphilis	6,750	32	51	14	3
68	Syphilitic arthritis	4,500	52	27	7	14
69	Charcot's joint	18,350	91		3	6
70	Charcot's joint	275	25	11	19	45
		600	28	32	9	31
71	Traumatic arthritis	3,550	10	2	42	46
72	Myocardial failure	320	24	26	10	38
73	Scurvy	200	20	18	46	16
74	Degenerative arthritis	600	88	8	4	

TABLE 9—*Results of Chemical Examination of Blood and Synovial Fluid in Miscellaneous Arthritis*

Case Number	Total Protein in Joint Fluid, Gm per 100 Cc	Nonprotein Nitrogen, Mg per 100 Cc		Sugar, Mg per 100 Cc		Cells, per C Mm
		Blood Plasma	Joint Fluid	Blood	Joint Fluid	
48 (Charcot)	3.4	26	30	125	139	160
69 (Charcot)	3.8	42	28	103	125	18,350
70 (Charcot)	4.0	32	26	60	87	275
67 (Syphilitic)	3.8	22	24	126	78	6,750

increased above that which is found in normal synovial fluid (chart 1). The lower values were observed in the miscellaneous group and in some of the cases of acute rheumatic fever and rheumatoid arthritis. On the average, the total amount of protein in the synovial fluid was higher in the infected fluids, that is, from persons with gonococcal and tuberculous arthritis. There was no correlation between the total nitrogen content of the fluid and the number of cells or the nonprotein nitrogen content of individual fluids. The amount of protein in the fluid from the joints depended to some extent on the degree and severity of the inflammatory process present.

TABLE 10—Summary of Results of Findings in Synovial Fluid in Ninety Cases of Arthritis Compared with Normal Synovial Fluid

	Total Number of Cells, per C. Min	Differential Cell Count, per Cent				Chemical Examination				Gonococcal Complement Fixation Test
		Poly morpho nuclears	Lympho cytes	Mono cytes	Clas mato cytes	Leucino phils	Total Protein, Gm per 100 Cc	Sugar, Mgr per 100 Cc	Nonprotein Nitrogen, Mgr per 100 Cc	
Normal fluid	±50	±5	?	±38	±30	?			15 to 40 Same as Blood	Negative
Gonococcal arthritis										
Infected fluid	7,000 to 138,000	76 to 99	1 to 14	1 to 7	1 to 12	1 to 2	16 to 59	52 to 99	16 to 38	Positive in
Noninfected fluid	1,000 to 78,000	16 to 100	1 to 12	1 to 2	1 to 22	1 to 2	35 to 60	38 to 138	16 to 40	74 per cent
Rheumatic fever	2,150 to 34,570	83 to 97	1 to 7	1 to 11	1 to 19		20 to 47	74 to 135	19 to 35	Negative
Rheumatoid arthritis	1,500 to 71,800	9 to 100	1 to 67	1 to 26	1 to 65	1 to 15	24 to 51	80 to 124	20 to 46	Negative
Tuberculous arthritis	6,500 to 110,000	59 to 91	3 to 26	2 to 26	1 to 7	1 to 3	16 to 55	79 to 160	16 to 22	Negative
Miscellaneous										
Charcot's	275 to 18,540	25 to 70	6 to 22	1 to 42	3 to 16		34 to 110	78 to 139	24 to 50	Negative
Syphilitic	4,200 to 4,550	17 to 52	35 to 71	7 to 2	3 to 16		38	78	21	
Scruvy	200	20	18	46	16					
Streptococcus	102,500 to 150,000	91 to 100	1	1	2					
Traumatic	600 to 3,550	10 to 88	2 to 8	1 to 12	0 to 16					
Myocardial failure with effusion in joints	520	21	26	10	38					

Bacteriologic Examinations—Bacteria were recovered in ten cases of gonococcic arthritis, three cases of hemolytic streptococcic arthritis and five cases of tuberculosis of the joints. These findings were of great assistance in the etiologic diagnosis of the disease. In all other cases, the fluid of the joints was sterile.

Total and Differential Cell Counts—The total cell counts of the various synovial fluids varied within wide limits. Infected fluids, such as those seen in hemolytic streptococcic infections, contained over 100,000

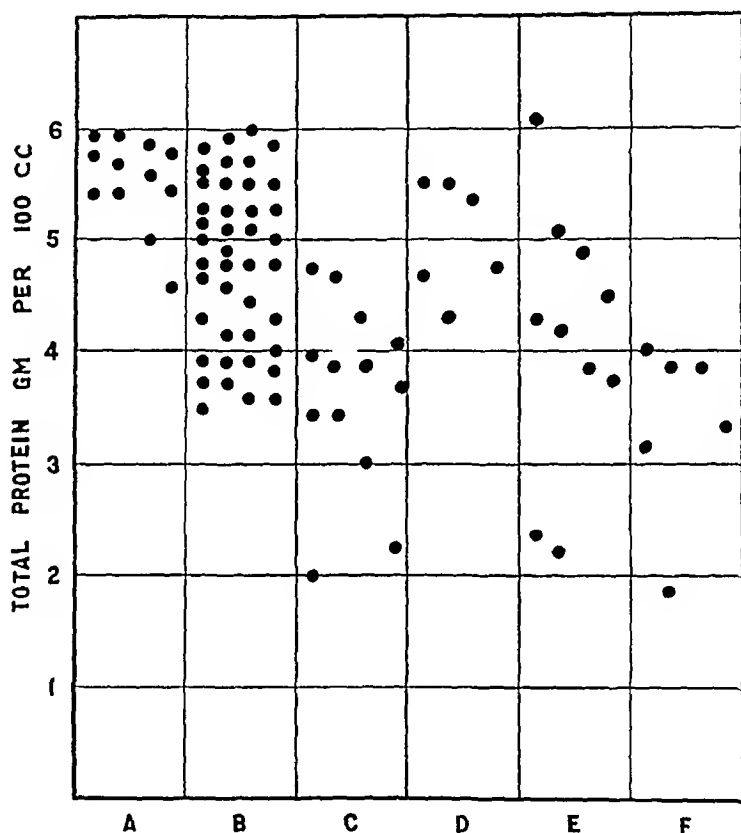


Chart 1—Total protein content of the synovial fluid in various types of arthritis. Each dot represents the total protein content of the synovial fluid from a patient who showed: *A*, gonococcic arthritis with infected fluid, *B*, gonococcic arthritis with noninfected fluid, *C*, rheumatic fever, *D*, tuberculous arthritis, *E*, rheumatoid arthritis, *F*, miscellaneous arthritides including Charcot joints and syphilitic arthritis.

cells per cubic millimeter, whereas those infected with gonococci seldom contained more than 60,000 per cubic millimeter. In spite of the fact that most of the synovial fluids were noninfected, the vast majority of samples contained less than 40,000 cells. The cases showing the lowest cell counts were those of traumatic arthritis and Charcot joints. In these the count was often less than 1,000 per cubic millimeter. From a study of the total cell counts in the other cases, it was not possible to show

wide variations in the different groups, so that, aside from the cases with very low counts and those with very high counts, the differences were, on the whole, slight

The differences in the differential counts were more striking than those in the total counts, as the noninfected fluids showed a greater number of monocytes, clasmatocytes and lymphocytes than did the infected fluids. This was particularly evident in the cases of rheumatoid arthritis and in the miscellaneous cases. In the infected fluids the polymorphonuclear cells were usually increased above 80 per cent, with the exception of the tuberculous fluids in which they varied from 46 to 93 per cent.

Nonprotein Nitrogen—The nonprotein nitrogen content of the synovial fluids varied within the same limits in all groups of cases. The amount could be correlated with the level of nonprotein nitrogen in the blood and not with any other factor, such as the total nitrogen content, cell count or presence or absence of infection. The determination of nonprotein nitrogen, therefore, was of no diagnostic significance.

Sugar Content of Synovial Fluid—The sugar content of the synovial fluids is shown in chart 2. The data show that the sugar content varied within the same range as the normal value for blood sugar without fasting, but in addition there were a number of instances in which the sugar content of the synovial fluid was below 70 mg per hundred cubic centimeters. On further analysis, it was found that the amount of sugar in the synovial fluids in all groups of cases depended on three factors: (1) the level in the blood at the time fluid was aspirated from the joint, (2) the number of leukocytes, and (3) the presence of microorganisms.

In some cases, the sugar level of the synovial fluid per hundred cubic centimeters was higher than that of the blood. This can be explained on the basis of the fact that the fluid was not aspirated after the patient had fasted, but frequently several hours after a meal, and it is known that the blood sugar level declines after a meal sooner than the synovial fluid sugar does. It is a matter of importance, then, to interpret the level of the sugar of the synovial fluid as normal, increased or decreased only when one knows the level of the blood sugar and the time in relation to meals that aspiration was performed.

It was found, further, that the level of the sugar of the synovial fluid could be correlated to some extent with the number of cells in the synovial fluid and the presence or absence of infection. The relation between the number of cells and the sugar content of the infected and noninfected fluids is shown in chart 2. Generally speaking, the presence of microorganisms and a high cell count were accompanied by a smaller amount of sugar in the synovial fluid. But, as the noninfected fluids with a high cell count also showed low values for sugar in the synovial

fluid, it was obvious that both the cell content and the presence of microorganisms were of significance in determining the level of the sugar of the synovial fluid. A low sugar content, then, did not always indicate infected fluid.

Gonococcic Complement Fixation Test—The results of the gonococcal complement fixation test of the blood serum and synovial fluid of patients with various types of arthritis were reported elsewhere.¹¹ Forty-eight samples of synovial fluid from twenty-seven patients with gonococcic arthritis were examined. The reaction was positive in thirty-one specimens of synovial fluids, doubtful in one and negative in sixteen. The reactions of the blood serum and synovial fluid, simultaneously

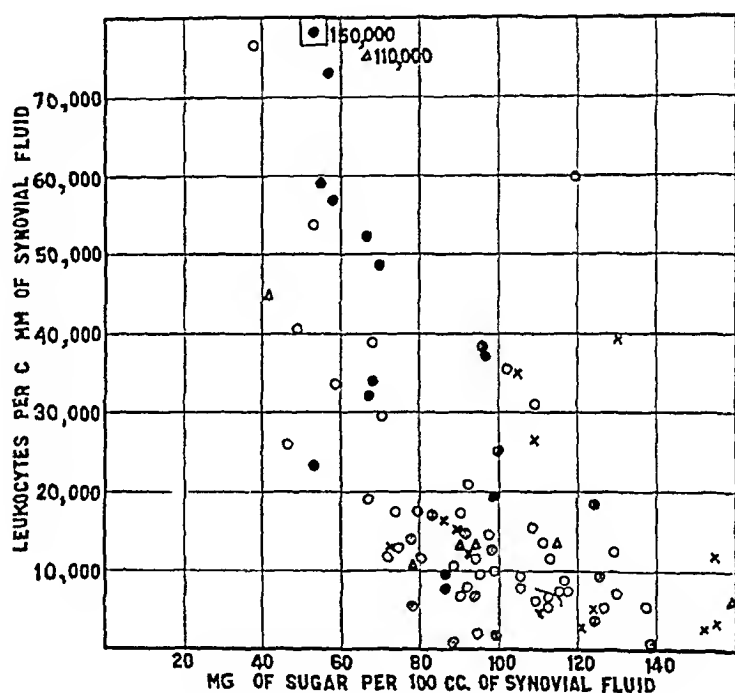


Chart 2—Total cell counts and sugar content of synovial fluid. Each symbol represents the sugar content per hundred cubic centimeters of synovial fluid from a patient with dot, gonococcic arthritis with infected fluid, circle, gonococcic arthritis with noninfected fluid, triangle, tuberculous arthritis, cross, rheumatic fever, cross within circle, rheumatoid arthritis, and dot within circle, miscellaneous arthritides.

collected, were identical except in six instances. The reaction of the synovial fluid was negative on four occasions when that of the blood serum was doubtful or positive. In one case, there was a doubtful gonococcic complement fixation reaction of the synovial fluid in association with a positive reaction in the blood serum, and another showed a positive reaction of the synovial fluid with an associated doubtful reaction of the blood serum. In three patients it was possible to observe the change of the reaction in the blood serum and synovial fluid from

negative to positive. The blood serum showed a positive gonococcic complement fixation reaction before the synovial fluid. In three patients, both the blood serum and the synovial fluid gave negative reactions early in the course of the disease when gonococci were recovered from the synovial fluid. The reaction was positive in six specimens of synovial fluid from four other patients with fluid infected by the gonococcus.

Fourteen specimens from twelve patients with rheumatic fever were likewise examined. One from a patient without evidence of gonococcic infection gave a positive reaction. On repeated examination the fluid gave a negative reaction. Sixteen specimens from ten patients with various other disorders of the joints not due to the presence of the gonococcus gave negative gonococcic complement fixation reactions.

TABLE 11—Results of the Wassermann Test in the Synovial Fluids from Sixty Cases of Arthritis

	Fluids					Number Disagreeing with Blood Serums
	Number of Patients	Number of Specimens	Number Plus	Number ±	Number Minus	
Gonococcal arthritis	29	19	1	0	48	3
Rheumatic fever	12	14	0	0	14	0
Rheumatoid arthritis	10	16	0	0	16	0
Syphilitic arthritis	2	4	3	1	0	1
Charcot joints	3	4	0	2	2	2
Miscellaneous	4	6	0	0	6	0
Total	60	63	4	3	86	6

Wassermann Reaction—The results of the Wassermann test of ninety-three specimens of synovial fluid from sixty patients are shown in table 11. The reactions of both the blood serum and the synovial fluid, simultaneously collected, were negative on eighty-four occasions. Four specimens of synovial fluid from two patients with syphilitic arthritis were examined. The blood serum and synovial fluid were positive on three occasions. Once the reaction of the blood serum was positive when that of the synovial fluid was doubtful. Two patients with Charcot joints due to tabes dorsalis were found to give a positive reaction in the blood serum and a doubtful reaction in the synovial fluid. The synovial fluids from two patients with gonococcic arthritis gave negative Wassermann reactions at the time that the reaction of the blood was positive. In one other patient with gonococcic arthritis the reaction of the synovial fluid was positive when that of the blood serum was negative.

COMMENT

From the data presented we now return to the question we set out to answer, namely, What information of diagnostic value may be obtained

from a study of the synovial fluid in patients with arthritis? Before discussing this question in the light of our material, it is necessary to review the information that exists regarding normal synovial fluid in order to compare the various characteristics of both normal and abnormal synovial fluids.

Under usual circumstances the amount of synovial fluid present in any of the joints is so small that its examination during life is impractical. Small amounts of fluid have been obtained by various observers³ during surgical procedures or after death. The results have been summarized by Forkner,⁴ who stated that the fluid usually consists of a few cubic centimeters of thick gelatinous material, containing from none to 50 cells per cubic millimeter, chiefly macrophages and small amounts of protein and mucin. It is known, however, from the recent observations of Bauer, Bennett, Marble and Clifton⁵ and Bauer, Bennett and Short⁶ on the synovial fluid from the normal joints of young beef cattle, that normal synovial fluid consists of a transudation of noncolloidal electrolytes and small amounts of protein from the blood plasma, together with a small amount of mucin. The approximate total protein content of this fluid was calculated to be 680 mg or 0.68 per cent per hundred cubic centimeters. The nucleated cells varied between 103 and 165 per cubic millimeter. The presence of red blood cells was considered to be the result of trauma. From the recent experiments of Vaubel,⁷ it is now proved that mucin is formed by the synovial cells grown in tissue culture.

Bearing these facts in mind, then, it is possible from the examination of synovial fluids in disease to determine in what respect they differ from the normal.

An increase in the amount of synovial fluid may be the result of transudation or exudation resulting from inflammation. Transudates into the cavities of the joints are observed under the same circumstances as they appear in other serous sacs, that is, with increased venous pressure, decrease of plasma protein or obstruction to lymphatic drainage. Thus, one finds effusions into the joints in cases of con-

3 Key, J. A. Cytology of Synovial Fluid in Normal Joints, *Anat. Rec.* **40**: 193, 1928.

4 Forkner, Claude. The Synovial Fluid in Health and Disease with Special Reference to Arthritis, *J. Lab. & Clin. Med.* **15**: 1187 (Sept.) 1930.

5 Bauer, W., Bennett, G., Marble, A., and Clifton, D. Observations on Normal Synovial Fluid of Cattle. I. The Cellular Constituents and Nitrogen Content, *J. Exper. Med.* **52**: 835 (Dec.) 1930.

6 Bauer, W., Bennett, G. A., and Short, C. L. Speculations on the Etiology of Rheumatoid Arthritis, *New England J. Med.* **208**: 1035 (May 18) 1933.

7 Vaubel, E. The Form and Function of Synovial Cells in Tissue Culture. II. The Production of Mucin, *J. Exper. Med.* **58**: 85, 1933.

gestive heart failure with edema of the extremities, in some cases with nephrotic edema or in thrombophlebitis of the femoral vein. Under these circumstances, the fluid has a low protein and cellular content. In the one case we studied, the cell count was 320 per cubic millimeter and clasmatocytes, monocytes and lymphocytes predominated. The protein content was low, 1.8 Gm per hundred cubic centimeters, and the non-protein nitrogen content was increased as it was in the blood. From the literature, summarized by Folkner,¹ it was stated that transudates were usually transparent, with a specific gravity varying from 1.008 to 1.018. The cells varied from 0 to 50, and were composed mostly of macrophages and mesothelial cells, the protein content was low. The diagnosis of a transudate is justifiable, then, when the synovial fluid has the characteristics just mentioned, or when a synovial effusion occurs in the presence of a disease in which there is transudation of fluid into the other tissues of the body.

When there is an inflammatory lesion of the synovial membrane with an effusion into the cavity of the joint, the characteristics of the fluid are different from normal synovial fluids or from transudates. It is this group of conditions that we studied, and the diagnostic significance of the changes may now be discussed.

From our observations it was plain that the most helpful examination in establishing an etiologic diagnosis of arthritis was the isolation of pathogenic micro-organisms from the synovial fluid. This was especially true in the cases of gonococcic, hemolytic streptococcic and tuberculous arthritis. In all other cases the synovial fluid was sterile.

Cytologic examinations of synovial fluid revealed the fact that during the course of an acute inflammatory lesion of the synovial membrane, the total cell count was increased and polymorphonuclear cells predominated. When the fluids were infected, the cells were commonly all polymorphonuclear. When they were not infected, the lymphocytes, monocytes and clasmatocytes were increased, and comprised between 10 and 60 per cent of the total number of cells. These changes are similar to those found in other effusions of the serous sacs, when the cytology of infected and noninfected fluids is studied.⁸ The presence, then, of a cellular reaction in the synovial fluid in which polymorphonuclear cells predominate is evidence of an infected fluid. In the case of tuberculous arthritis, this is not necessarily true as the polymorphonuclear cells may not predominate in all cases. A low cell count with a high percentage of macrophages and clasmatocytes indicates a non-infected fluid.

⁸ Scott, T. F. M. and Finland, M. The Cytology of Pleural Effusions in Pneumonia Studied with a Supravital Technique, *Am J M Sc* **188** 322, 1934.

The gonococcic complement fixation test was of distinct value in the etiologic diagnosis of gonococcic arthritis. This was particularly true in a few patients who had no signs of an active genital infection at the time of the arthritis, but who had a history of a previous infection. This was of interest in view of the previous observation of Forkner,⁹ who found gonococci in the lymph nodes of a patient with chronic arthritis eight years after a genital infection, with no active localized genital infection at the time of examination. In our experience, the test was positive in 74 per cent of the synovial fluids examined. These results are in accord with the observations of others.¹⁰ When the blood serum and synovial fluid were examined simultaneously, it was found that the results of the test were in agreement. Occasionally, the blood serum showed a positive reaction before the synovial fluid. In no case was a positive reaction found in the synovial fluid and a negative reaction in the blood, although the results were not necessarily of the same intensity. In view of the negative results in other types of arthritis and the rare occurrence of falsely positive reactions, the test was of assistance in the diagnosis of gonococcic arthritis.

The Wassermann reaction of the synovial fluid provided positive information in the rare cases of syphilitic arthritis. In these cases it is usually positive in both the blood and the synovial fluid, whereas, in the cases of Charcot joints in tabes dorsalis, the reaction may be positive in the blood and negative in the synovial fluid. Since gonococcic and syphilitic infections frequently coexist, the rôle of both infections may be difficult to interpret as far as the arthritis is concerned. However, the presence of a positive Wassermann reaction in the blood and synovial fluid, together with the type of cellular reaction which is characterized by an increase in the number of lymphocytes, monocytes and plasmatocytes, is highly suggestive of active syphilitic arthritis.

The nonprotein nitrogen content of the synovial fluid was of no diagnostic significance in discriminating infected from noninfected fluids or transudates from exudates. The values were the same in both the blood and the synovial fluid, indicating a transudation of the electrolytes from the blood plasma into the synovial cavity.

9 Forkner, C. Material from Lymph Nodes. III. Gonococci from Lymphoid Tissue in a Case of Chronic Infectious Arthritis, *Bull. Johns Hopkins Hosp.* **32**: 257 (Oct.) 1928.

10 Holbøll, S. A. Gonorrheal Arthritis, Particularly with Regard to the Complement Fixation Reaction for Gonorrhea, *Hospitaltid* **73**: 18 (Jan. 2) 1930. Blin, A. S. The Complement Fixation Reaction in Gonorrhea, *Acta med. Scandinav. (supp.)* **50**: 332, 1932. Green, F. Complement Fixation in Gonorrheal Arthritis, *Canad. M. A. J.* **28**: 289 (March) 1933. Kling, D. H., and Pincus, J. The Gonococcus Complement Fixation Test in Synovial Fluid, *J. Lab. & Clin. Med.* **17**: 39 (Oct.) 1931.

We said previously that normal synovial fluid and transudates into the synovial cavities contain only small amounts of protein. In the cases reported, the total protein content was increased above normal in both the infected and the noninfected fluids from patients with gonococcal arthritis, rheumatoid arthritis, acute rheumatic fever and tuberculous arthritis and in the miscellaneous group of cases. The presence, therefore, of an increased amount of protein in the synovial fluid indicated only an exudate and not the actual presence of infection.

It has been stated that a low sugar content of the synovial fluid is indicative of an infection of the joints,¹¹ although Pemberton¹² pointed out that the sugar level may be low in noninfected fluids with a high cellular content. We found that both of these factors were significant and that the level of the blood sugar was also of importance in interpreting synovial fluid values. It was not possible from a sugar determination alone to discover whether or not infection was present.

SUMMARY AND CONCLUSIONS

One hundred and twenty samples of synovial fluid from ninety patients with various types of arthritis were studied to determine the diagnostic significance of the various biologic and chemical characteristics of the fluid.

1 The bacteriologic examination of the fluids yielded information of the greatest value in the etiologic diagnosis of arthritis. Inoculation of guinea-pigs with the synovial fluid was helpful in the diagnosis of tuberculous arthritis.

2 The results of the gonococcal complement fixation and Wassermann tests of the blood and synovial fluids were in agreement. Both tests were of distinct aid in the etiologic diagnosis of disease of the joints.

3 The total cell count of the synovial fluid was increased in all the types of arthritis studied. It was highest in the infected fluids and lowest in the cases of Charcot joints and traumatic arthritis. Most noninfected fluids contained less than 40 000 cells per cubic millimeter.

4 When the synovial fluid was infected with micro-organisms, the polymorphonuclear cells were greatly increased, from 86 to 100 per cent, and the lymphocytes, monocytes and clasmatocytes were few in number. In tuberculosis of the joints, the polymorphonuclear count varied from 46 to 93 per cent, and the lymphocytes and monocytes were increased.

11 Allison, Fremont-Smith, Dailey and Kenard -^b Key³

12 Pemberton, R. A. *Arthritis and Rheumatoid Condition*, Philadelphia, Lea & Febiger, 1929, p. 129.

5 The percentages of lymphocytes, clasmatoocytes and monocytes were always higher in the noninfected fluids than in the infected fluids. The presence of a low cell count with an increase in the monocytes, lymphocytes and clasmatoocytes was an indication of a noninfected fluid.

6 The chemical examination of the fluids yielded no information of diagnostic value in discriminating between infected and noninfected fluids. The nonprotein nitrogen of both the infected and the noninfected synovial fluids was the same as that of the blood. The sugar content varied with the presence of organisms, the number of cells and the level of the sugar in the blood. A low sugar content did not always mean an infected fluid. The total protein value of the synovial fluid was increased in both groups, and indicated only an inflammatory reaction.

7 Aside from the bacteriologic, cytologic and serologic examinations of the synovial fluid, other tests yielded little information of diagnostic value.

CALORIGENIC ACTION OF SINGLE LARGE DOSES OF DESICCATED HOG THYROID

COMPARISON WITH THE ACTION OF THYROXINE GIVEN
ORALLY AND INTRAVENOUSLY

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Several reports have recently been made from this clinic concerning the effects of administering thyroxine in various forms orally and intravenously in an alkaline solution ¹ These observations have shown that single doses of from 10 to 100 mg of pure thyroxine administered by mouth or duodenum do not have a demonstrable effect on the basal metabolism of patients with myxedema, whereas the oral administration of single large doses of monosodium thyroxine and thyroxine in alkaline solution causes increases in the basal metabolism of 22 and 63 per cent respectively, as great on the average as the increase produced by the intravenous injection of an alkaline solution It seemed important to determine the effect of single large doses of desiccated thyroid of the same iodine content for comparison with these data We have previously

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1 (a) Thompson, W O , Thompson, P K , and Dickie, L F N Monosodium Thyroxine, Desiccated Thyroid and an Impure Sodium Salt of Thyroxine Comparison of Their Effects When Administered Orally with the Effect of Thyroxine Injected Intravenously in an Alkaline Solution, Arch Int Med **52** 576 (Oct) 1933 (b) Thompson, W O , Thompson, P K , Dickie, L F N , and Alper, J M Effect of Alkali on the Absorption of Thyroxine from the Gastro-Intestinal Tract, *ibid* **52** 809 (Nov) 1933 (c) Thompson, W O , Thompson, P K , Taylor, S G , III, Alper, J M , and Dickie, L F N The Effect of Various Compounds of Thyroxine on the Basal Metabolism Endocrinology **18** 228, 1934 (d) Thompson, W O , Thompson, P K , Dickie, L F N , and Taylor, S G III The Iodine in the Thyroid Gland, West J Surg **41** 431 (Aug) 1933 (e) Thompson, W O , Thompson, P K , Taylor, S G , III, and Dickie, L F N Oral and Duodenal Administration of Single Large Doses of Pure Thyroxine Comparison of Calorigenic Effects with Those of Monosodium Thyroxine and Thyroxine in Alkaline Solution, Arch Int Med **54** 818 (Nov) 1934

reported observations which suggest that the oral administration of desiccated thyroid and the intravenous injection of thyroxine in doses which contain the same total amounts of iodine produce equal increases in the basal metabolism, when the comparison is made on the basis of the quantities of the two substances that have to be administered every day in order to hold the basal metabolism of patients with myxedema at the normal level ²

METHOD

Five patients with myxedema ³ were used for this study, and in four of them the effects of giving thyroxine in various ways have also been determined. In patients 1, 3 and 5 the myxedema was spontaneous, in the second patient it followed a subtotal thyroidectomy for exophthalmic goiter, and in the fourth patient, a subtotal thyroidectomy for a nontoxic nodular goiter. Various parts of the data on the first three patients have been published, as they were collected ⁴ to illustrate other points.

The desiccated thyroid was hog thyroid (Wilson's) containing 0.23 per cent iodine and was used in the form of 1 grain (0.065 Gm.) tablets. All of the thyroid was from one lot except that given to the fifth patient. Since the mode of administration, particularly with reference to food, may be important, these details are incorporated in the legends of the charts.

For all the patients, curves are recorded showing the complete effect on the basal metabolism of each administration of desiccated thyroid or of thyroxine. These curves not only show the amount of increase in the basal metabolism, but make it possible to calculate roughly, by a method previously described,⁵ the total number of excess calories produced.

The monosodium salt of synthetic thyroxine was administered in the form of tablets each of which contained 1.03 mg. of the salt.

The Sanborn-Benedict and Benedict-Roth machines were used in making the basal metabolism determinations, and Aub-DuBois standards were used in the calculations.

² Thompson, W. O., McLellan, L. L., Thompson, P. K., and Dickie, L. F. N. The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man. The Relation Between the Iodine in Desiccated Thyroid and in Thyroxine, *J. Clin. Investigation* **12** 235 (Jan.) 1933.

³ All of the data on the fifth patient and most of the data on the fourth patient were collected at the Cook County Hospital, the remainder, at the Rush Medical College and at the Presbyterian Hospital. Dr. Frederick Tice and Dr. Karl A. Meyer allowed us to collect the data at the Cook County Hospital.

⁴ Thompson, W. O., Alper, J. M., Thompson, P. K., and Dickie, L. F. N. The Effect of Diiodotyrosine on the Basal Metabolism in Myxedema, *J. Clin. Investigation* **13** 29, 1934, footnote ^{1b}.

⁵ (a) Thompson, W. O., Thompson, P. K., Brailey, A. G., and Cohen, A. C. The Calorigenic Action of Thyroxine at Different Levels of Basal Metabolism in Myxedema, *J. Clin. Investigation* **7** 437 (Aug.) 1929. (b) Thompson, McLellan, Thompson and Dickie ².

DATA

The data are recorded in charts 1 to 5 and summarized in tables 1 and 2. In order to facilitate comparison, the effects of all the doses of desiccated thyroid and of thyroxine have been calculated in terms of 6.5 mg of iodine by the method indicated in the footnotes to the tables. It may be noted that the effect of a given dose of desiccated thyroid varied somewhat from patient to patient. Thus, by calculation, the smallest absolute increase in basal metabolism for doses containing 6.5 mg of iodine was 15 points (from minus 26 to minus 11 per cent) and the greatest, 28 points (from minus 39 to minus 11 per cent), while the average increase was 22 points (from minus 37 to minus 15 per cent). The number of excess calories produced by the same

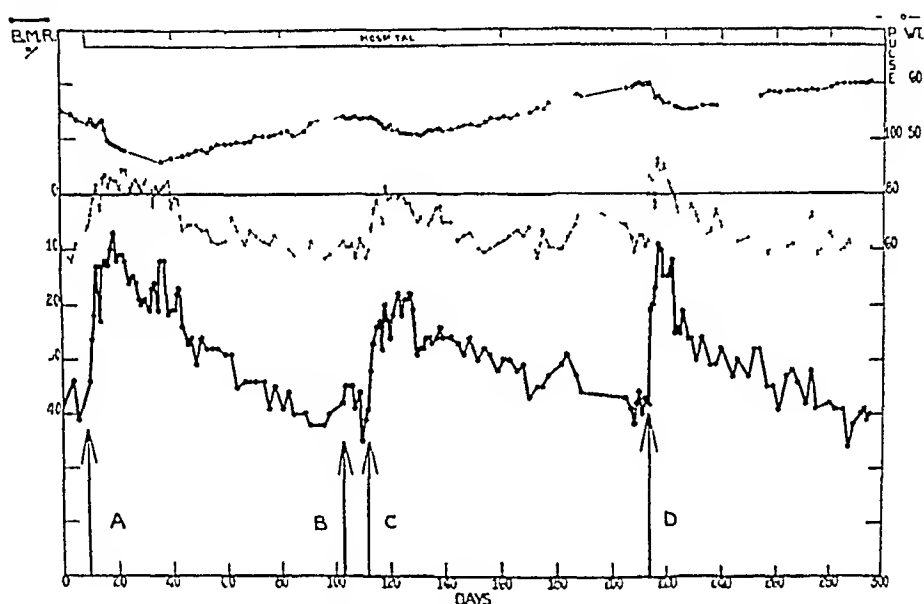


Chart 1—Comparison of effects of a single large dose of desiccated thyroid with those of thyroxine given orally and intravenously in a patient with myxedema (Mrs. M. M., height, 159 cm., age, 58). *A* indicates intravenous administration of 10 mg. of synthetic thyroxine in alkaline solution, *B*, oral administration of 10 mg. of synthetic thyroxine in distilled water, *C*, oral administration of 10 mg. of synthetic thyroxine in alkaline solution, *D*, oral administration of 275 Gm. of desiccated thyroid. Details of the three administrations of thyroxine have been published.^{1b} The dose of 275 Gm. (42.4 grams) of desiccated thyroid was given at 11:20 a. m. on April 30, 1933, the patient having had no food since 6 o'clock the night before. A total of 250 cc. of distilled water was used to wash down the tablets.

dose varied from 3,260 in the third patient to 9,795 in the fourth patient. The average number was 7,405.

In the first four patients the effect of giving thyroxine intravenously in alkaline solution was also observed. In the first patient the increase in basal metabolism produced by the oral administration of 275 Gm.

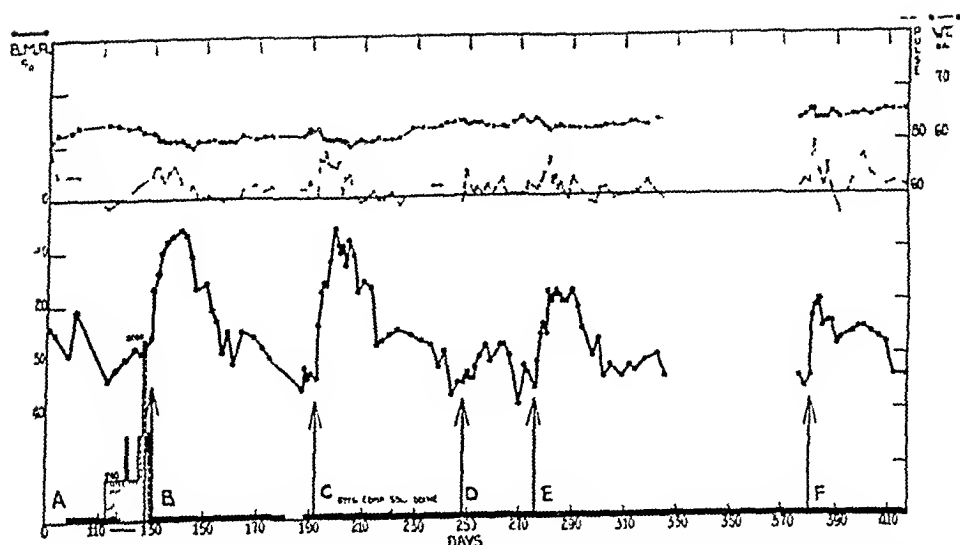


Chart 2—Comparison of the effects of a single large dose of desiccated thyroid with those of thyroxine given orally and intravenously in a patient with myxedema (Mrs A R, height, 160 cm, age, 33) The treatment was as follows intravenous administration (A) of diiodotyrosine (in milligrams), (B) of 75 mg of synthetic thyroxine in alkaline solution and (C) of 75 mg of natural thyroxine in alkaline solution, oral administration (D) of 75 mg of synthetic thyroxine in the form of the monosodium salt, (E) of 75 mg of synthetic thyroxine in alkaline solution and (F) of 205 Gm of desiccated thyroid Details of the various administrations of thyroxine have been published^{1b} The dose of 205 Gm (317 grains) of desiccated thyroid was given at 4 20 p m on April 24, 1933, the patient having had lunch about four hours before A total of 250 cc of distilled water was used to wash down the tablets

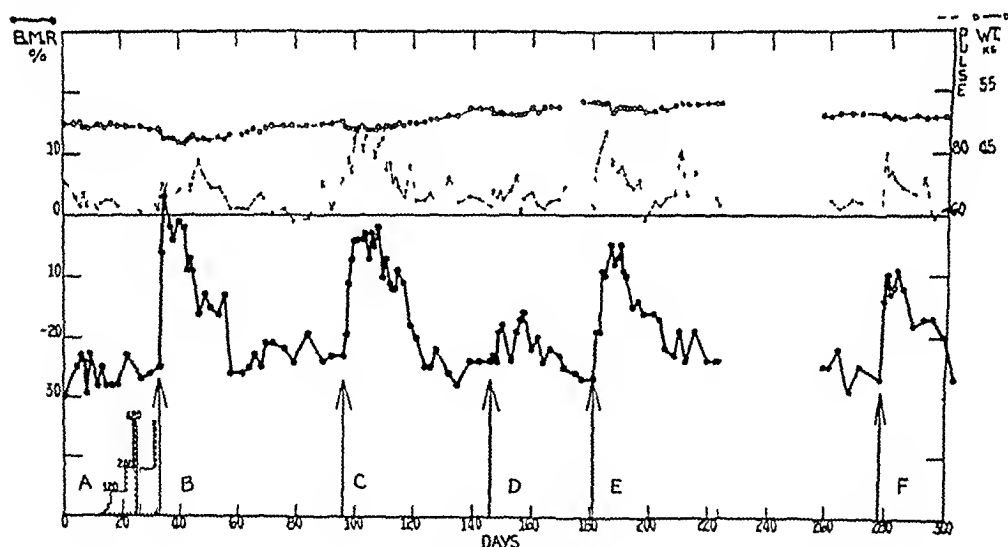


Chart 3—Comparison of the effects of a single large dose of desiccated thyroid with those of thyroxine given orally and intravenously in a patient with myxedema (Mrs M K, height, 152 cm, age, 36) Treatment was as follows intravenous administration (A) of diiodotyrosine in milligrams, (B) of 10 mg of synthetic thyroxine in alkaline solution and (C) of 10 mg, of natural thyroxine alkaline solution, oral administration (D) of 10 mg of synthetic thyroxine in form of the monosodium salt, (E) of 10 mg of synthetic thyroxine in alkaline solution and (F) of 275 Gm of desiccated thyroid Details of the various administrations of thyroxine have been published^{1b} The dose of 275 Gm of desiccated thyroid was given at 11 a m on April 10, 1933, the patient having fasted since 6 o'clock the night before A total of 250 cc of distilled water was used to wash down the tablets

(42.4 grains) of desiccated thyroid containing 63 mg of iodine (from minus 39 to minus 12 per cent) was about the same as that produced by the intravenous administration of 10 mg of thyroxine containing 65 mg of iodine (from minus 40 to minus 11 per cent). In patients 2, 3 and 4 the increases produced by desiccated thyroid were less than those produced by giving thyroxine intravenously, the increases being, respectively, 59, 68 and 84 per cent as great. In other words, in some patients the effect of a single large dose of desiccated thyroid may be nearly twice as great as in others when the comparison is made with

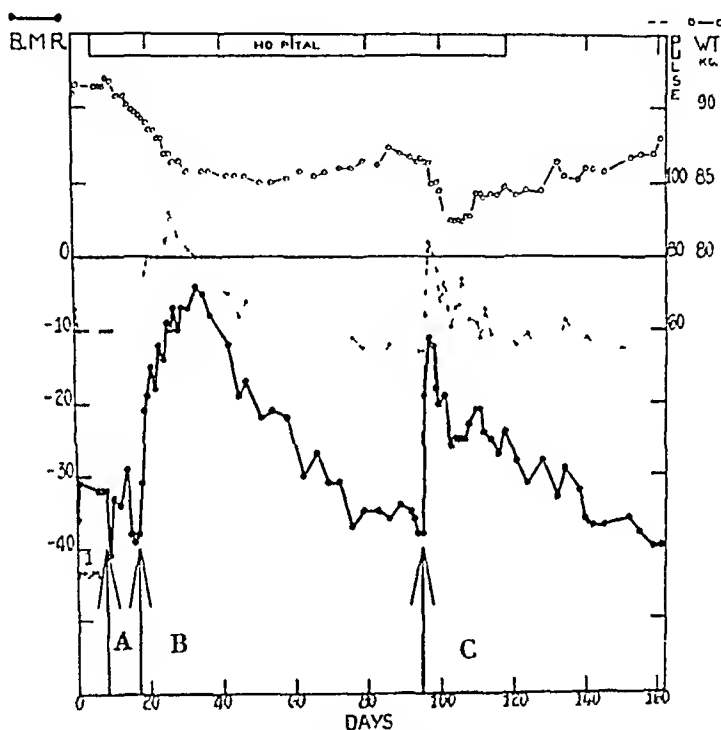


Chart 4—Comparison of effects of oral administration of a single large dose of desiccated thyroid with those of intravenous administration of a single large dose of thyroxine in a patient with myxedema (Mrs C F, height, 163 cm, age, 44). An intravenous injection of 1 mg of synthetic thyroxine (A) was made at 4:25 p.m. on Feb. 2, 1933, the thyroxine being dissolved with the aid of potassium hydroxide. An intravenous injection of 10 mg of synthetic thyroxine (B) was made at 4:18 p.m. on February 11, the thyroxine being dissolved by the addition of 4 drops of a 10 per cent solution of potassium hydroxide to its suspension in distilled water. It was sterilized for injection by placing the test tube which contained it in a beaker of boiling water for twenty minutes. A dose of 2.75 Gm of desiccated thyroid (C) was administered at 2:45 p.m. on April 30, the patient having had dinner at 11:20 a.m. A total of 500 cc of distilled water was used to wash down the tablets.

the effect of an intravenous dose of thyroxine containing the same amount of iodine. The increase from desiccated thyroid in all four

patients was 76 per cent as great on the average as that produced by thyroxine given intravenously

In the first three patients we have also observed the effects of giving thyroxine by mouth in a solution of sodium hydroxide and in the form of its monosodium salt (tablets) In the first patient the increase in basal metabolism produced by giving thyroxine in alkaline solution was less than that produced by giving a dose of desiccated thyroid containing about the same amount of iodine but in the second and third patients the effect was greater On the average, for quantities containing 65 mg of iodine, the thyroxine given by mouth

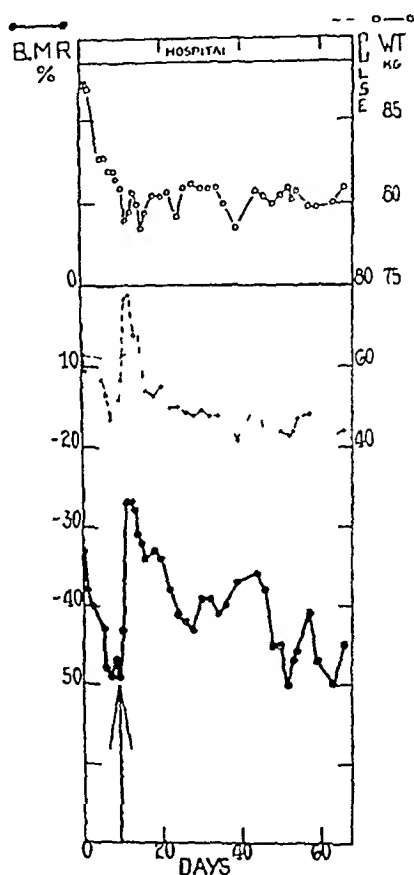


Chart 5—The effect of oral administration of a single large dose (275 Gm) of desiccated thyroid to a patient with myxedema (Mr G H, height, 194 cm, age, 54) The administration was made at 5 p m on May 12, 1933, shortly after supper, a total of 500 cc of distilled water being used to wash down the tablets

in an alkaline solution produced an increase in basal metabolism of from minus 34 to minus 13 per cent in the three patients, and desiccated thyroid caused an increase of from minus 33 to minus 13 per cent, while thyroxine given intravenously in an alkaline solution to the same three patients produced an increase of from minus 32 to minus 5 per cent Thus the changes produced by the oral administration of desiccated thyroid and by an alkaline solution of thyroxine were almost the

TABLE 1—Comparison of Effects on Basal Metabolism of Single Large Doses of Desiccated Thyroid with Those of Thyroxine Given Both Orally and Intravenously

Patient	Medication	Total Iodine Content of Substance Used, Mg	Basal Metabolic Rate Before Medication, per Cent of Normal	Level to Which Basal Metabolic Rate Rose, per Cent of Normal	Change in Basal Metabolic Rate, Points	Time Required for Maximum Change in Basal Metabolic Rate, Days	Length of Time Basal Metabolic Rate Was Affected, Days	Time Occupied by Descending Portion of Metabolic Curve, Days	Number of Excess Calories Produced	Change in Terms of Response to Intravenous Injection of 10 Mg of Thyroxine in Alkaline Solution*	
										On Basis of Increase in Basal Excess Metabolic Rate, per Cent	On Basis of Increase in Basal Excess Metabolic Rate, Produced, per Cent
Mrs M M	10 mg of synthetic thyroxine in alkaline solution, intravenously	6.3	-40	-11	29	9	80	66	14,860	100	100
	10 mg of pure synthetic thyroxine suspended in distilled water, by mouth	6.3	-40	-33	5	1	8	5	310	17	2
	10 mg of synthetic thyroxine in alkaline solution, by mouth	6.3	-40	-19	21	6	95	80	12,030	72	81
	2.75 Gm (42.4 grains) of desiccated thyroid (tablets), by mouth	6.3	-39	-12	27	1	69	64	9,005		
	Calculated effect of 2.83 Gm † desiccated thyroid by mouth	6.3	-39	-11	28				9,265	97	62
	7.5 mg of synthetic thyroxine in alkaline solution intravenously	1.9	-40	-7	23	6	15	32	6,910		
Mrs A R	7.5 mg of natural thyroxine in alkaline solution, intravenously	1.9	-31	-9	25	7	53	41	9,000		
	Average effect of 7.5 mg of thyroxine in alkaline solution, intravenously	1.9	-32	-8	21	6	49	37	7,935		
	Calculated effect of 10 mg of thyroxine† in alkaline solution, intravenously	6.3	-32	0	32				10,605	100	100
	7.5 mg of synthetic thyroxine in form of its monosodium salt (tablets), by mouth	1.9	-36	-29	7	6	27	10	1,825		
	Calculated effect of 10 mg of synthetic thyroxine in form of its monosodium salt, by mouth	6.3	-36	-27	9				2,435	28	2
	7.5 mg of synthetic thyroxine in alkaline solution, by mouth	1.9	-35	-19	16	5	42	28	4,980		
	Calculated effect of 10 mg. of synthetic thyroxine in alkaline solution, by mouth	6.3	-35	-14	21				6,635	66	63

Mrs M K	2.07 Gm (31.7 grains) of desiccated thyroid (tablets), by mouth	17	-35	-21	14	2	34	31	4,385	
	Calculated effect of 2.83 Gm of desiccated thyroid, by mouth	65	-35	-16	19				6,075	59
	10 mg of synthetic thyroxine in alkaline solution, intravenously	65	-26	-1	25	2	29	22	5,115	
	10 mg of natural thyroxine in alkaline solution, intravenously	65	-23	-4	19	1	29	17	4,700	
	Average effect of 10 mg of thyroxine in alkaline solu- tion, intravenously	65	-25	-3	22	3	29	20	4,720	100
	10 mg of synthetic thyroxine in form of its mono- sodium salt (tablets), by mouth	65	-25	-19	6	3	25	14	1,07	28
	10 mg of synthetic thyroxine in alkaline solution, by mouth	65	-26	-6	20	6	33	24	4,315	91
	2.75 Gm (42.4 grains) of desiccated thyroid (tablets), by mouth	63	-26	-11	15	2	33	26	3,170	
	Calculated effect of 2.83 Gm of desiccated thyroid, by mouth	65	-26	-11	15				3,260	69
	10 mg of synthetic thyroxine in alkaline solution (potassium hydroxide), intravenously	65	-38	-6	32	10	77	59	19,110	100
Mr G H	2.75 Gm (42.4 grains) of desiccated thyroid (tablets), by mouth	63	-38	-12	26	2	60	57	9,520	
	Calculated effect of 2.83 Gm of desiccated thyroid, by mouth	65	-38	-11	27				9,795	50
	2.75 Gm (42.4 grains) of desiccated thyroid (tablets), by mouth	63	-48	-27	21	2	17	41	8,110	
	Calculated effect of 2.83 Gm of desiccated thyroid, by mouth	65	-48	-26	22				8,655	

* For each patient the figures in the first column under this heading have been calculated by dividing the number of points the metabolism increased following each type of treatment by the number of points by which it increased following the intravenous administration of 10 mg of thyroxine and multiplying the result by 100. The figures for the second column have been calculated in a similar manner.

† For all the patients the increase in basal metabolism following the administration of desiccated thyroid has been changed to terms of 6.5 mg of iodine by multiplying the number of points by which it increased by the fraction $\frac{2.83}{\lambda}$ in which λ = the dose of desiccated thyroid used. Excess calories have been changed in a similar manner.

‡ The effects of the various doses of thyroxine in this patient have been changed to terms of 10 mg by multiplying the number of points the basal metabolism increased following their use by the fraction $\frac{10}{7.5}$.

same, but in the two patients (second and third) in whom the comparison was made, the effect of each was about from two to three times as great as that produced by the oral administration of the monosodium salt of thyroxine (from minus 31 to minus 23 per cent on the average)

There are some differences between the curves for desiccated thyroid and those for thyroxine. In the first four patients the maximum increase in basal metabolism appeared to occur proportionately more quickly following the oral administration of single large doses of desiccated thyroid (three days on the average) than following the intravenous administration of large doses of thyroxine (seven days on the average). In the first three patients the maximum increase also occurred more quickly following the oral administration of desiccated thyroid (three days on the average) than following the oral administration of thyroxine in alkaline solution (six days on the average). In patients 1 and 4 the maximum increase in metabolism was sustained for a shorter period following the oral administration of desiccated thyroid than following the intravenous administration of thyroxine, with the result that the total number of excess calories produced by desiccated thyroid was less than would be expected from the increase in basal metabolism. In the second and third patients, on the other hand, the number of excess calories produced by desiccated thyroid was roughly proportional to the increase in basal metabolism. In the first four patients the effect of desiccated thyroid was only 60 per cent as great, on the average, as that of thyroxine given intravenously, when the comparison was made on the basis of the number of excess calories produced, as compared with 76 per cent when the comparison was made on the basis of the increase in basal metabolism. This difference in the average effect was caused chiefly by the fact that in the first and fourth patients the effect of desiccated thyroid was only 62 and 50 per cent as great, respectively, as that of thyroxine given intravenously on the basis of excess calories, as compared with 97 and 84 per cent, respectively, on the basis of increase in the basal metabolism. The reason for this difference is unknown.

When the metabolism had shown its maximum change and had begun to decrease, the rate of change seemed to be similar for both desiccated thyroid and thyroxine. In the first four patients the average time represented by the descending portion of the curve for metabolism was forty-five days following the administration of large doses of desiccated thyroid, and forty-six days following the intravenous injection of thyroxine. In the first three patients the corresponding times for oral administration of desiccated thyroid, oral administration of thyroxine in alkaline solution and intravenous administration of thyroxine in alkaline solution were, respectively, forty, forty-four and forty-one days.

The higher the metabolism before treatment, the shorter is the duration of the effect, a phenomenon which appears to influence chiefly the number of excess calories produced rather than the absolute increase in the basal metabolism. Thus the increase in basal metabolism following the administration of 2.75 Gm of desiccated thyroid (63 mg of iodine) in the fifth patient was the same as that following the intravenous injection of 10 mg of thyroxine (65 mg of iodine) in the third patient, but a longer period was required for the basal metabolism to return to its level before treatment in the fifth patient because of its greater initial depression, and hence the number of excess calories was greater. Two observations which we have previously reported are pertinent to the interpretation of all data showing the calorigenic effect of thyroxine and of desiccated thyroid.

1. At levels of metabolism below the normal the effect of thyroxine given intravenously every day appears to be roughly proportional to the dose when the dose is not sufficient to raise the rate above the normal.²

2. A given dose of thyroxine has much less effect when the metabolism is normal before administration than when it is markedly reduced (minus 40 per cent).^{5a}

Following every administration of single large doses of desiccated thyroid and of thyroxine the maximum clinical improvement was observed while the metabolism was falling, and in every instance the clinical condition of the patient was much better when the metabolism reached its premedication level than before any treatment was given.

It is of interest to combine the data of this paper with those previously reported in other parts of this study. This has been done in table 2. The comparisons made in this table seem to be justified because the initial depression of the basal metabolism was nearly the same for most types of treatment. It may be noted that, on the average, the increases in basal metabolism produced by the oral administration of monosodium thyroxine, thyroxine in alkaline solution and desiccated thyroid are, respectively, 22, 63 and 69 per cent as great as that produced by giving thyroxine intravenously in alkaline solution. In terms of excess calory production, the corresponding figures would be 18, 58 and 48 per cent, respectively. Thus, on the basis of equal iodine contents, the effect of oral administration of single large doses of desiccated thyroid is nearly the same, on the average, as that of oral administration of thyroxine in alkaline solution, while each produces from about two and one-half to three times as much effect as oral administration of monosodium thyroxine.

COMMENT

The reason for the variation in effect of a given dose of desiccated thyroid from patient to patient is not clear. Since most of the thyroid

TABLE 2—Summary of Effects of Single Large Doses of Desiccated Thyroid and of Thyroxine

Medication*	Total Iodine Content of Substance Used, Mg	Number of Patients	Number of Administrations	Average Basal Metabolic Rate Before Treatment, per Cent of Normal	Average Level to Which Basal Metabolic Rate Rose, per Cent of Normal	Average Change in Basal Metabolic Rate, Points	Average Number of Excess Calories Produced	Change in Terms of Average Response to Intravenous Injection of 10 Mg of Thyroxine in Alkaline Solution	
								On Basis of Increase in Basal Metabolic Rate, per Cent	On Basis of Excess Calories Produced, per Cent
10 mg § of pure synthetic thyroxine suspended in distilled water, by duodenum	6.5	3	3	-30	-29	1		3	
10 mg ¶ of pure synthetic thyroxine suspended in distilled water, by mouth	6.5	1	1	-32	-30	2		6	
10 mg ¶ of synthetic thyroxine in form of its monosodium salt (tablets), by mouth	6.5	6	6	-28	-21	7		22	
Patients receiving monosodium salt by mouth, in whom excess calories were calculated	6.5	1	1	-30	-22	8	2,755	23	18
10 mg # synthetic thyroxine in alkaline solution, by mouth	6.5	5	5	-31	-11	20		63	
Patients receiving thyroxine in alkaline solution by mouth, in whom excess calories were calculated	6.5	1	1	-31	-12	22	9,010	69	58
2.83 Gm ** of desiccated thyroid (tablets), by mouth	6.5	5	5	-37	-15	22	7,405	69	48
10 mg *** of thyroxine in alkaline solution, intravenously	6.5	6	8	-37	-5	32	15,520	100	100

* The effect of a given dose of thyroxine was changed to terms of 10 mg by multiplying the number of points the basal metabolism changed following its administration by the fraction $\frac{10}{\text{dose}}$ in which dose = the dose of thyroxine used. All thyroxine referred to in this table was the synthetic (Hoffmann-La Roche) except that so called natural thyroxine (Squibb's) was used for four of the intravenous injections.

† The figures in this column were calculated by dividing the number of points by which the basal metabolism increased following treatment by 32 and multiplying the result by 100.

‡ The figures in this column were calculated by dividing the number of excess calories produced by each type of treatment by 15,520 and multiplying the result by 100.

§ The doses used were 10 mg, 40 mg, and 50 mg.

¶ The doses used were 10 mg, 20 mg, 40 mg, and 100 mg.

The doses used were four of 10 mg each, one of 30 mg, and one of 10 mg.

** For all the details of the administration of desiccated thyroid, see table 1.

*** All the doses were 10 mg, except two of 7.5 mg. Sodium hydroxide was used to dissolve the thyroxine for all administrations except one, in which potassium hydroxide was used (Mrs. C. F., table 1).

used was from one lot, the difference can scarcely be attributed to variation in potency, and some other explanation must be sought. The facts that the effect of thyroxine in alkaline solution is only 63 per cent as great on the average when given by mouth as when given intravenously and that desiccated thyroid has about the same effect, on the average, as thyroxine in alkaline solution when each is given by mouth suggest that some of the active principle of both is destroyed in the gastro-intestinal tract or fails to be absorbed. The data suggest that the process which is responsible for failure of absorption probably varies from patient to patient.

The variation in absorption which results in a variation from patient to patient in the ratio of the calorigenic action of desiccated thyroid by mouth from that of thyroxine given intravenously shows that comparisons of different preparations of desiccated thyroid with one another and with thyroxine in different patients may lead to erroneous conclusions and emphasizes the desirability of comparing the effects of different preparations in the same patient.

Since when small daily doses are given over a long period, the effects of desiccated thyroid by mouth and of thyroxine intravenously appear to be the same on the basis of equivalent iodine contents, it is possible that absorption is more efficient when desiccated thyroid is given in small daily doses than when it is administered in single large doses.

SUMMARY

In five patients with myxedema the oral administration of single doses of desiccated thyroid caused an increase in basal metabolism of from minus 37 to minus 15 per cent on the average, and the production of 7,405 excess calories on the average for every 65 mg. of iodine.

In four patients in whom the comparison was made, the calorigenic effect of the oral administration of a single large dose of desiccated thyroid varied from 59 to 97 per cent (average, 76 per cent) of the effect of intravenous administration of a single large dose of thyroxine containing the same amount of iodine when the comparison was made on the basis of the increase in basal metabolism, and from 50 to 69 per cent (average 60 per cent) when the comparison was made on the basis of the number of excess calories produced.

In three patients in whom the comparison was made, the increases in basal metabolism produced by these large doses of desiccated thyroid were from 75 to 133 per cent as great as those produced by the oral administration of thyroxine in alkaline solution on the basis of equal iodine contents, and on the average the effects of the two were approximately the same.

If the data of the present study are combined with those previously reported, it is found that on the average the increases in basal metabolism produced by the oral administration of monosodium thyroxine, thyroxine in alkaline solution and desiccated thyroid are, respectively, 22, 63 and 69 per cent as great as that produced by the intravenous injection of thyroxine. If the comparison is made on the basis of excess calories produced, the corresponding figures are, respectively, 18, 58 and 48 per cent.

MYASTHENIA GRAVIS ASSOCIATED WITH THYMOMA

REPORT OF TWO CASES WITH AUTOPSY

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Since Weigert¹ first described the presence of a thymoma in a case of myasthenia gravis, reports of this association have become increasingly frequent, and great interest has been aroused in its significance. We have been fortunate in observing two patients with myasthenia gravis in whom thymomas were found at necropsy. Alter and Osnato² suggested "that all cases of myasthenia gravis with definite pathologic observations should be recorded, not only for the reason of their rarity, but that they may serve toward the construction of an explanation of the pathology of the disease, confirm part of it or offer useful hints for future observation." For these reasons the following cases are reported.

REPORT OF CASES

CASE 1—History—K. F., a Greek housewife, aged 27, was admitted to the Lenox Hill Hospital from the ophthalmologic dispensary on Dec 19, 1932, complaining of drooping of both eyelids. Three weeks before admission, she had suffered from a mild attack of influenza. At that time she also had a transient weakness of the left arm. Shortly thereafter, she noticed a drooping of the left upper eyelid, which was followed in rapid succession by involvement of the right eyelid and complete inability to move either eyeball. She occasionally "saw double."

Her history was essentially unimportant except for an attack of acute articular rheumatism ten years before, which had lasted for one month. Her menses were normal. She was married and had three children. One daughter, aged 2 years, was deaf and dumb.

Physical Examination—Physical examination revealed an obese white woman who was not acutely ill. The pulse rate was 88, the temperature, 99.8 F, the respiratory rate, 20, and the blood pressure, 120 systolic and 80 diastolic. Her face had a masklike expression. Partial ptosis of both eyelids, complete bilateral

From the medical service of Dr. A. L. Garbat and the Achelis Laboratory of the Lenox Hill Hospital.

1 Weigert, C. Pathologisch-anatomischer Beitrag zur Erbischen Krankheit, *Neurol. Centralbl.* 20: 594, 1901.

2 Alter, N. M. and Osnato, M. Myasthenia Gravis with Status Lymphaticus and Multiple Thymic Granulomas, *Tr. Am. Neurol. A.* 55: 303, 1929.

external ophthalmoplegia and paralysis of convergence were present. The pupils were equal and slightly irregular, and reacted sluggishly to light and distance. The fundi and visual fields were normal. There was a marked fetor ex oris, and many teeth were missing. The tonsils were enlarged and cryptic, and contained cheesy material. The heart, lungs and abdomen were normal. The reflexes were active and equal, and no pathologic reflexes were elicited. The sensorium was intact.

Laboratory Data—Examination of the blood revealed red cells, 5,000,000, hemoglobin (Sahli), 85 per cent, white cells, 8,250, neutrophils, 79 per cent, and lymphocytes, 21 per cent. Blood chemistry showed urea nitrogen, 10.8 mg per hundred cubic centimeters, creatinine, 0.5 mg, uric acid, 2.8 mg, sugar, 74 mg, carbon dioxide-combining power, 55.7 volumes per cent, serum calcium, 10.6 mg per hundred centimeters, and serum phosphorus, 3.7 mg. The Wassermann reaction of the blood was negative. The cerebrospinal fluid, obtained by lumbar puncture, was clear and under normal pressure, it contained 2 leukocytes and 1 red blood cell per cubic millimeter and 57 mg of sugar per hundred cubic centimeters. The globulin, Wassermann and colloidal gold tests were negative. Routine urinalysis gave negative results except for the presence of calcium oxalate crystals. Determination of the total creatinine excreted in a twenty-four hour specimen of urine revealed 0.54 Gm. A sugar tolerance test (100 Gm of dextrose orally) gave the following results:

	Blood Sugar Mg per 100 cc	Urine Sugar Mg per 100 cc
Fasting	94	Neg
45 min after dextrose	266	0.3
2 hrs after dextrose	270	1.0

Roentgenograms of the skull and chest showed no abnormality. On stimulating the biceps and peroneus muscles with faradic current, the strength of response showed a progressive diminution in marked contrast with that of normal controls of the same age group.

Course—The initial diagnosis was postinfluenzal epidemic encephalitis. The patient was treated symptomatically with a preparation of potassium iodide, sodium salicylate, strychnine and caffeine. By the early part of February, a change in the clinical picture was evident. General asthenia was progressive and extreme. The patient complained of dizziness, generalized body pains and headaches. Not only was she completely bedridden, but she was unable to lift her head from her pillow. There was such marked fatigue of the jaws on chewing and dysphagia that it became necessary to feed her through a duodenal tube. There was almost no masseter or temporal muscle action, and she tired quickly on talking. Though normal at first, her speech would take on a mumbling and lisping character after a few minutes. A slight right facial weakness was noted (fig 1).

On Feb 14, 1933, she was seen by Dr Foster Kennedy, who made the diagnosis of myasthenia gravis on the basis of the bizarre clinical picture. She was given $\frac{3}{8}$ grain (0.375 Gm) of ephedrine sulphate twice daily, which resulted in a slight improvement in her condition. She looked brighter and began to move her upper eyelids slightly.

On March 5, the patient suddenly collapsed. Marked inspiratory distress was present. The respirations were chiefly abdominal, and the nostrils were dilated. She became cyanotic, the palpebral fissures were widened, the pupils were dilated and did not react to light, and no pulse was felt at the wrists. On stimulation with epinephrine, caffeine and metrazol, and with oxygen furnished through a nasal

catheter she rallied and in several hours was no longer dyspneic or cyanotic. The pulse rate was 112 and regular. That day the temperature, which throughout the whole course of the illness had been normal, rose to 100.6 F.

The next morning the patient appeared brighter and oxygen was temporarily discontinued. Her pulse rate was not very forceful, but it was regular. The heart sounds were of fair quality. The blood pressure was 120 systolic and 85 diastolic. The lungs were clear, except for occasional crepitant rales at both bases.

On March 7, two days after her initial collapse, dyspnea and cyanosis suddenly recurred, and she complained of a choking sensation. She sank rapidly and, in spite of artificial respiration and stimulation by epinephrine and caffeine, died.

Necropsy—**Macroscopic Examination** The body was that of an obese white woman, 150 cm. in length. The pupils were equal and slightly irregular, and were in mid-dilatation. Livor and rigor mortis were marked.

The skull was not examined. The pleural cavities contained no free fluid. The right lung lay free in the pleural cavity and weighed 325 Gm. The pleural surface was smooth and glistening, except for extensive purplish-red, slightly depressed

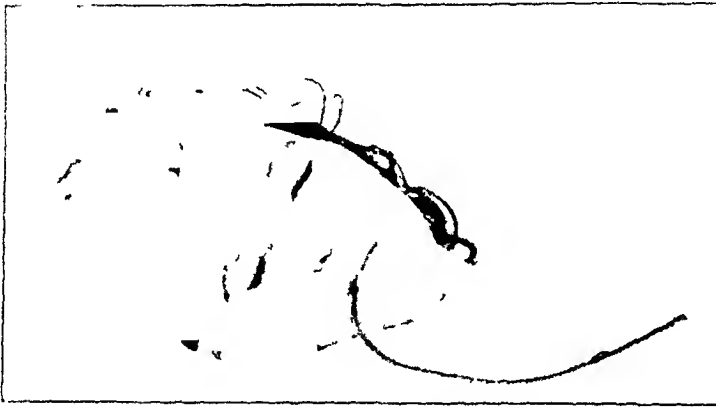


Fig. 1 (case 1)—Photograph showing the masklike facies, ptosis of the eyelids, and right facial weakness.

areas over the lower lobe. On section, the lung was edematous and reddish brown. The portions of the lung beneath the depressed areas were beefy red and urless. The left lung was firmly adherent to the chest wall at its apex and weighed 250 Gm. It was similar to the right lung in appearance and on section.

The pericardial sac contained no excess fluid. The heart was small, weighing 225 Gm. The surface was smooth and glistening. There was a moderate amount of epicardial fat. On section, the myocardium was reddish brown. The valves, aorta and coronary arteries showed no gross abnormalities.

In the anterior mediastinum was a mass, apparently composed of two structures, extending down the anterior surface of the pericardium. The upper half had the appearance of a hyperplastic thymus gland, except that it was somewhat firmer than normal. The lower half, rising from the inferior pole of the gland, was a firm, oval, encapsulated nodular mass, measuring approximately 4 cm. in its longest and 2.5 cm. in its shortest diameter. On section, it was grayish white and trabecular and contained several small areas of calcification.

The thyroid and parathyroid glands were grossly normal.

The anterior abdominal wall measured 5.5 cm. in thickness, only 0.5 cm. of which was muscle. The muscle fibers were dull brown. The diaphragm was

extremely thin and almost translucent. The peritoneal cavity contained no excess fluid. The liver weighed 1,600 Gm. Its capsule was smooth and not thickened. On section, it was congested and reddish brown. The gallbladder and bile ducts appeared to be normal.

The spleen weighed 200 Gm. The capsule was smooth and not thickened, and the surface was dark red. On section, the pulp was soft and congested. Malpighian corpuscles were visible.

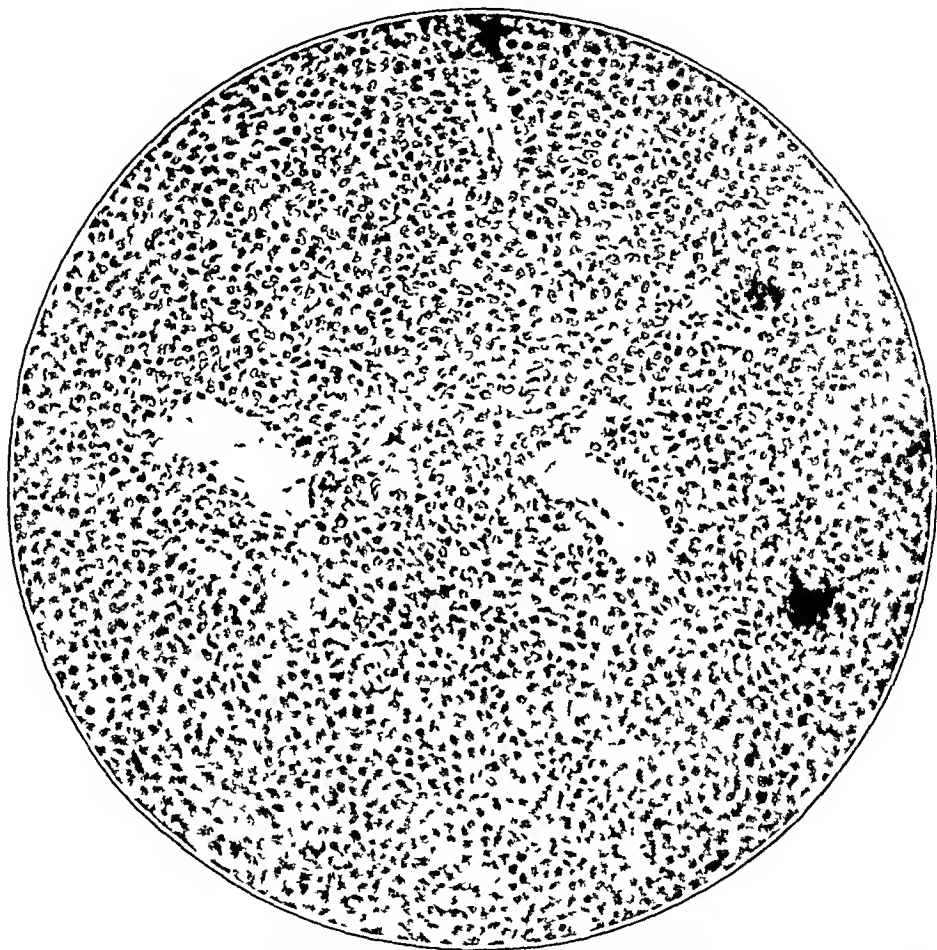


Fig 2—Photomicrograph of a section of thymoma, showing the anastomosing sheets of polyhedral cells and the scanty lymphocytes. Hematoxylin and eosin stain, $\times 200$.

The left kidney weighed 125 Gm. The capsule was smooth and was stripped with ease. The surface was reddish brown, streaked with yellow opaque areas. On section, it had the same mottled appearance and was deeply congested. The cortex was of normal thickness and the cortical markings were distinct. The right kidney weighed 150 Gm and was similar in appearance to the left.

The other viscera exhibited no gross abnormalities.

Anatomic Diagnosis There were congestion, edema and atelectasis of the lungs, atrophy of the heart, hyperplasia of the thymus gland, thymoma, atrophy of the skeletal muscles, and congestion of the liver, spleen and kidneys.

Microscopic Examination Sections through the upper portion of the mediastinal mass showed it to be the thymus gland. The lower circumscribed mass had the typical structure of a thymoma. It was completely encapsulated by a thick layer of dense hyaline fibrous tissue which contained occasional small focal collections of round cells. The blood vessels in the capsule exhibited moderate irregular knoblike hyperplasia of the intima. Sections from different portions of the tumor showed a somewhat varied picture. For the most part, it was composed

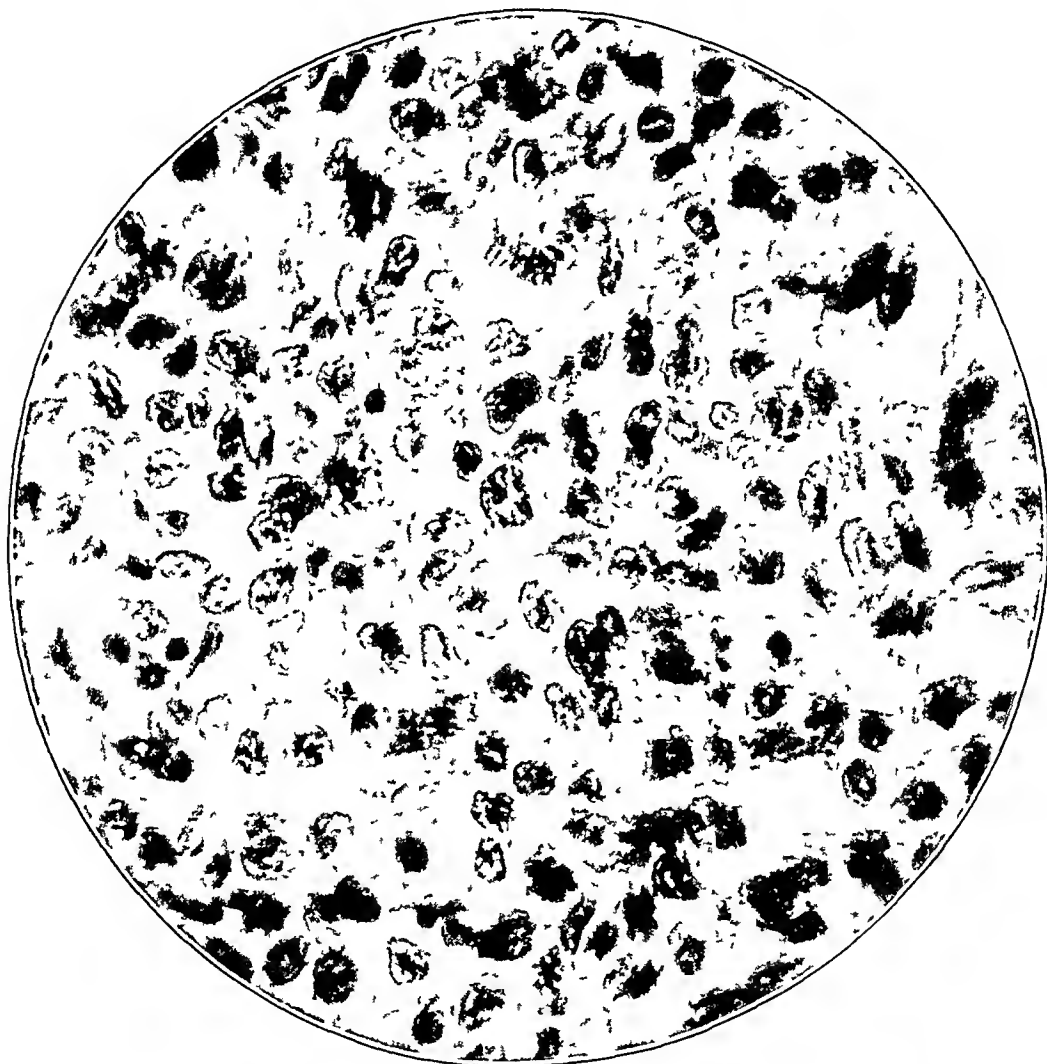


Fig 3—Photomicrograph of the same portion of tumor as shown in figure 2 under high power magnification. Hematoxylin and eosin stain, $\times 850$

of large anastomotic sheets of polyhedral cells, separated by small amounts of vascular fibrous tissue (fig 2). These cells had large vesicular nuclei and definite nucleoli. The cytoplasm was acidophilic and granular, and the cell outlines were indistinct. Some of the cells had a flattened appearance (fig 3). Small round cells were scanty and were situated mainly about the blood vessels. In other areas, large amounts of dense, fibrous stroma divided the tumor cells into irregular islands, and round cells were more conspicuous. In still other areas, the structure approached that of the thymus gland, round cells predominating over the thin cords of polyhedral cells (fig 4). The latter lay adjacent to the capillaries

Mitoses were infrequent. No plasma cells, eosinophils, giant cells or Hassall's corpuscles were seen.

Marked edema, congestion and large areas of atelectasis were noted in the lungs.

A deposit of anthracotic pigment, edema and slight endothelial hyperplasia were present in a bronchial lymph node.

The muscle fibers of the heart were thin and atrophic, and many showed an increased amount of pigment about the nuclei. The striations were indistinct,

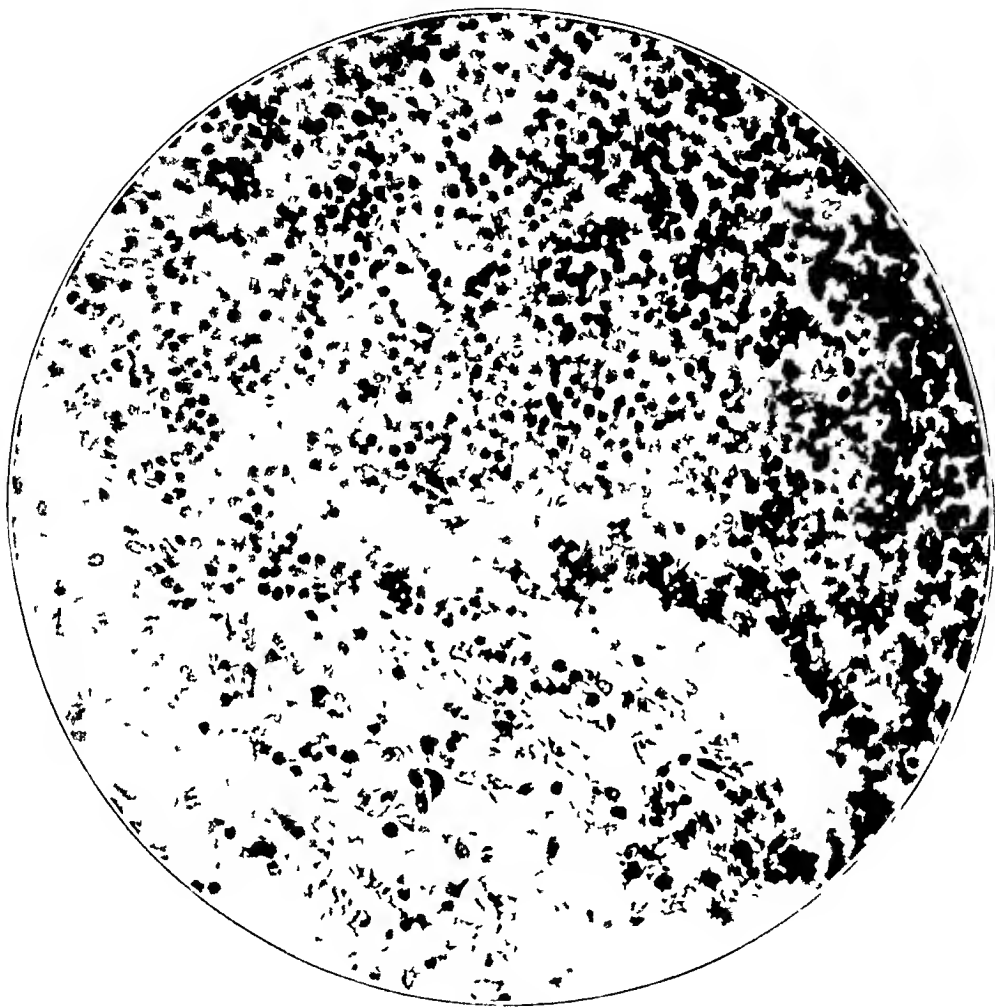


Fig 4—Photomicrograph of a section of the same tumor, showing the resemblance of areas to the thymus gland. Hematoxylin and eosin stain, $\times 200$.

and diffuse hyaline degeneration was present. Occasionally a muscle fiber was necrotic and in these areas there were localized collections of round cells (fig 5). The stroma was slightly increased and was edematous.

The liver cells were small and atrophic, and were the seat of an advanced fatty degeneration. In areas, the cell outlines were indistinct, and early necrosis was visible. The sinuses were diffusely and widely dilated. Kupffer cells were prominent, and some of them contained cellular detritus.

In the spleen the fibrous trabeculae were somewhat thickened. The veins, especially those within the trabeculae, were greatly congested. The reticulum

was moderately thickened in areas. The sinuses contained an increased number of polymorphonuclear leukocytes, and the endothelium was hyperplastic. The pulp was irregularly edematous and showed scattered neutrophils and small amounts of hemosiderin pigment, both free and within the large mononuclear cells. The arterioles exhibited rather advanced hyalinization of their walls and narrowing of their lumens. The malpighian corpuscles contained an occasional secondary nodule.



Fig 5—Photomicrograph of a section of cardiac muscle, showing a lymphorrhage about a necrotic fiber. Hematoxylin and eosin stain, $\times 400$.

In the kidneys intense congestion and small hemorrhages were present, especially in the medulla, where many of the collecting tubules were filled with blood. Degeneration of the tubular epithelium was slight. In the suprarenal glands the cortical cells exhibited marked vacuolar degeneration which involved practically all the cells, but was most marked in the inner layers. Many of the cells of the zona reticularis were completely necrotic and had disappeared, giving these areas a glandlike appearance. Many of the remaining cells were deeply pigmented. There were intense congestion and many small hemorrhages, especially in the zona reticularis. The medulla was normal except for edema.

The pancreas appeared to be normal except for autolysis. There was no evidence of abnormality in the uterus or ovaries, except a few small hemorrhages and edema of the endometrium. The thyroid showed a slight increase in the colloid, with flattening of the acinose cells. The parathyroids appeared to be normal. Examination of striated muscle from the abdominal wall and diaphragm showed the fibers to be atrophic. The nuclei were often arranged along the periphery of the fibers, and occasional small collections of round cells (lymphorrhages) were present between them.

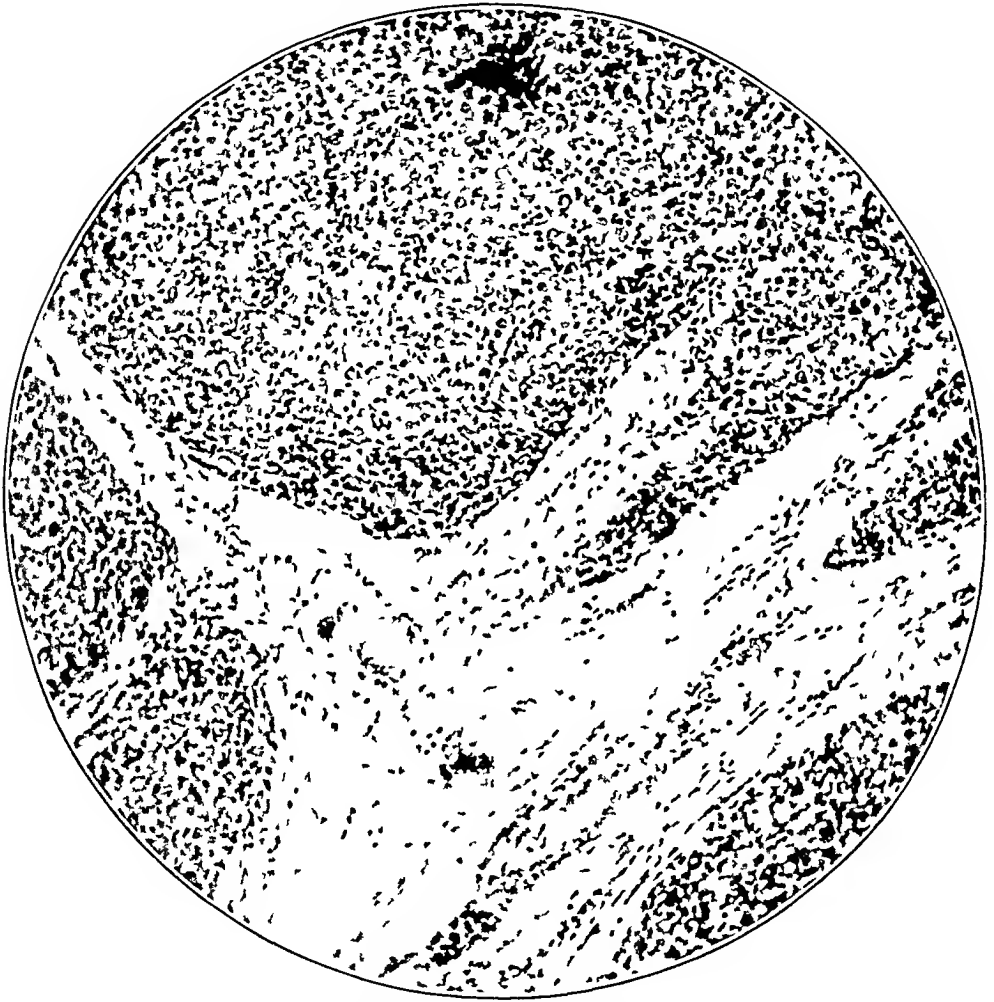


Fig. 6—Photomicrograph of a section of thymoma, showing the lobulation of the tumor by dense bands of fibrous tissue. Hematoxylin and eosin stain, $\times 200$.

CASE 2—History—L. K., a Lithuanian, aged 54 years, was admitted to the Gouverneur Hospital on Dec. 9, 1932, complaining of extreme weakness. For the past year he had been under treatment at the allergy clinic for frequent attacks of asthma. About one month before admission, he became extremely weak and was unable to talk consecutively for any length of time without his voice becoming inaudible. He had a heavy feeling in his head and also a feeling of warmth at times. About three weeks before admission he "lost his appetite for sleep," so that for several days he had not slept, day or night. There had been a moderate loss of weight in the past month.

Physical Examination—The temperature was 99.6 F, respiratory rate 20, the pulse rate 80, and the blood pressure, 192 systolic and 108 diastolic. The face was expressionless, and a slight ptosis of both upper eyelids was present. The pupils were equal and regular, and reacted to light and in accommodation. The fundi were normal. No ocular palsy was demonstrated. Conjunctival anesthesia and corneal hypesthesia were present. The apex beat of the heart was in the sixth interspace within the midclavicular line. The sounds at the apex were booming in quality. No murmurs were audible. The respiratory excursions were small, with prolonged expiratory murmur. Occasional sibilant and sonorous râles were heard over both lungs. Examination of the abdomen gave negative results. The abdominal and radioperiosteal reflexes were absent. The knee jerk reflexes were elicited by reinforcement. There were no pathologic reflexes or sensory disturbances. Coordination was good, and there was no ataxia.

A lumbar puncture revealed clear fluid which contained but 1 cell per cubic millimeter. The globulin test gave negative results. Six drops of the spinal fluid reddened Benedict's solution. Reactions to the Wassermann and Kahn tests were negative. The colloidal gold curve was 0001122322.

A few hours after admission, the patient died suddenly.

Necropsy—*Macroscopic Examination* The body was that of a well developed and well nourished white middle-aged man, 154 cm in length. The pupils were equal and regular and were in mid-dilatation. Rigor mortis was absent. The brain and its coverings were apparently normal. The right lung was densely adherent at the apex and weighed 380 Gm. The left lung lay free in the pleural cavity and weighed 300 Gm. There was an old scar at the right apex, and a moderate emphysema of the anterior borders of each upper lobe was seen.

The region of the thymus was occupied by a very dense, encapsulated, sausage-shaped mass, measuring 9 by 3 cm. It lay transversely across the trachea, great vessels and upper attachments of the pericardium. It was difficult to cut, and its surface presented a lobulated structure. The lobules were creamy yellow, and were separated by dense bands of fibrous tissue.

The pericardial sac contained no excess fluid. The heart weighed 300 Gm, and its surface was smooth and glistening. The left ventricle was moderately hypertrophied. The aorta and the left coronary artery exhibited a few atheromatous plaques. The valves were grossly normal. The myocardium was light brown.

The liver weighed 1,530 Gm. Its capsule was not thickened, and the cut surface was reddish brown. The gallbladder and bile ducts showed no gross abnormalities.

The spleen weighed 150 Gm, and on section the pulp was congested and soft.

The kidneys weighed 130 Gm each. The capsules were stripped with some difficulty and revealed a fine granular surface. On section, the cortices were slightly narrowed and the markings blurred. The blood vessels were prominent.

The other viscera exhibited no gross abnormalities.

Anatomic Diagnosis There were chronic adhesive pleuritis, pulmonary emphysema, hypertrophy of the left ventricle, atherosclerosis of the aorta and left coronary artery, thymoma, congestion of the liver and spleen and arteriosclerotic nephritis.

Microscopic Examination Sections through the mediastinal tumor showed it to be completely encapsulated by a thick layer of dense fibrous tissue from which wide trabeculae radiated into its substance, giving it a lobulated appearance. The trabeculae had a peculiar arrangement, branching off the main trunk like the limbs of a tree. The parenchyma was composed of large polyhedral or flattened reticular cells (fig 6). Lymphocytes were scanty, and only an occasional plasma cell was present.

The brain, lungs, liver and spleen were normal, except for congestion. The heart showed hypertrophy of muscle fibers, moderate degeneration and small focal collections of round cells.

The kidneys exhibited an advanced arteriolosclerosis, with many glomeruli in various stages of replacement by fibrous tissue. Slight degenerative changes were present in the tubular epithelium.

The suprarenal capsule was somewhat thickened. The cortical cells showed a marked vacuolar degeneration, especially in the zona fasciculata. In some areas the degeneration had progressed to actual necrosis of the cells. Marked hyperemia, numerous small hemorrhages and large collections of hemosiderin pigment were present, especially in the zona reticularis.

COMMENT

A perusal of the literature reveals that the diagnosis of myasthenia gravis frequently offers great difficulties. Because visual symptoms are usually the first to appear, an ophthalmologist is consulted before an internist. The initial diagnosis is frequently encephalitis. Both of our cases were so diagnosed. The difficulty in differentiating between the two conditions is further enhanced by the fact that cases of epidemic encephalitis simulating myasthenia gravis have been reported.³ However, if the possibility of myasthenia gravis is borne in mind, the simultaneous occurrence of a large number of incongruous changes soon makes the diagnosis of encephalitis untenable. As in case 1, the absence of fever and disturbance of sleep, the normal spinal fluid, the bizarre clinical picture of normal reflexes and sensorium, associated with muscular weakness, and the quick fatigue on chewing and talking, with recovery after rest, lead to the recognition of the malady. In addition, various laboratory procedures have been advocated as diagnostic aids.

A number of workers (Pierchalla,⁴ Mella,⁵ Reuter,⁶ and Keschner and Strauss⁷) reported a shadow in the region of the thymus shown by roentgen rays in cases of myasthenia gravis. Based on the frequent association of a thymoma in this disease such a finding would support the diagnosis. However, the absence of a shadow is of no significance, as many cases without this tumor have been described, also, when it actually is present, a roentgenogram of the chest can fail to reveal it. This point was well demonstrated in case 1.

3 Grossman, M. Epidemic Encephalitis Simulating Myasthenia Gravis, *J Nerv & Ment Dis* **55** 32, 1922.

4 Pierchalla, L. Ueber die Rontgenbehandlung der hyperplastischen Thymus bei Myasthenia pseudoparalytica, *Therap Halbmonatsh* **16** 504, 1921.

5 Mella, H. Irradiation of the Thymus in Myasthenia Gravis, *M Clin North America* **7** 939, 1923.

6 Reuter, A. Zur Kenntnis der Myasthenia gravis, *Deutsche Ztschr f Nerven* **120** 131, 1931.

7 Keschner, M., and Strauss, I. Myasthenia Gravis, *Arch Neurol & Psychiat* **7** 337 (March) 1927.

The so-called myasthenic or Jolly reaction, first described by Jolly⁸ in 1895, makes possible a more accurate determination of the fatigability of the skeletal muscles, and is of service in the early or mild cases.

Williams and Dyke,⁹ Hart¹⁰ and Nielsen and Roth¹¹ observed a diminished sugar tolerance in myasthenia gravis. The test performed in case 1 gave a typical diabetic curve.

A diminished urinary excretion of creatinine in myasthenia was reported by Williams and Dyke⁹ and by Monrad-Krohn and Forsberg.¹² According to Peters and Van Slyke,¹³ the level of total creatinine excretion in twenty-four hours in a normal person is constant and is dependent on his size and muscular development. It may be expressed in the form of a creatinine coefficient $\frac{\text{mg total creatinine in 24 hour specimen of urine}}{\text{body weight, kg}}$. Normally, the coefficient, based on total creatinine, ranges between 14 and 22 in women. It was 8.4 in case 1.

According to Noyes,¹⁴ lymphohemages can be demonstrated in the skeletal muscles in about 86 per cent of the cases of myasthenia gravis. In obscure cases, a biopsy of the skeletal muscle may be advisable.

There are two other diseases, syphilis of the central nervous system and tumor of the brain, which must be considered in the differential diagnosis. The former can be excluded by the negative reaction of the blood and spinal fluid to the Wassermann test and the normal gold curve, and the latter by the absence of localizing signs, the normal spinal fluid and roentgenograms of the skull.

The prognosis in this disease must always be guarded. Sudden death in the form of respiratory failure has been frequently reported but not sufficiently stressed.

The outstanding pathologic changes in myasthenia gravis are the abnormalities of the thymus and the so-called lymphohemages of the skeletal muscles.

The association of abnormalities of the thymus with myasthenia gravis is more than an accidental finding. Stann, quoted by Bell,¹⁵ in

8 Jolly, F. Ueber Myasthenia gravis pseudoparalytica, Berl klin Wchnschr **32** 1, 1895.

9 Williams, B. W., and Dyke, S. C. Observations on Creatinuria and Glycosuria in Myasthenia Gravis, Quart J Med **15** 269, 1921.

10 Hart, H. H. Myasthenia Gravis with Ophthalmoplegia and Constitutional Anomalies in Sisters, Arch Neurol & Psychiat **18** 439 (Sept.) 1927.

11 Nielsen, J. M., and Roth, P. Myasthenia Gravis. Report of Three Cases, J Nerv & Ment Dis **67** 32, 1928.

12 Monrad-Krohn, G. H., and Forsberg, R. Contribution to the Pathology of Myasthenia, Acta psychiat et neurol **5** 247, 1930.

13 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932.

14 Noyes, A. P. A Case of Myasthenia Gravis with Certain Unusual Features, Rhode Island M. J., **13** 52, 1930.

reviewing two hundred and fifty autopsies of myasthenia gravis, noted that a pathologic condition of the thymus was recorded in 28 per cent of the cases. Bell¹⁵ collected reports of all cases with autopsy from 1901, when Weigert¹ first described a thymic tumor in association with myasthenia gravis, to 1917. He found that the thymus was definitely abnormal in 49 per cent of the cases. Of the 49 per cent, hyperplasia was noted in 30 per cent, and thymoma in 19 per cent of the cases. Since 1917, no large group of cases which came to autopsy has been reported. The literature contains a considerable number of case reports, but most of them are of cases which did not come to autopsy. It is thus difficult to state the exact proportions of thymic tumors in myasthenia gravis with any degree of accuracy. It is conceivable that they are present in a greater percentage of cases than Bell's figures indicate.

Moreover, it is frequently difficult to determine when the thymic hyperplasia has assumed the characteristics of a thymoma. As in our two cases, the tumor is usually of moderate size, is definitely encapsulated and exhibits no metastases, unless the lymphorrhages in the muscles are considered as such. On section, it is cream or lemon yellow in color and often shows dense fibrous trabeculations. Microscopically, the parenchyma is composed of lymphocytes, plasma cells and large polyhedral cells. The last-mentioned cells resemble, and are supposedly derived from, the reticular cell. Occasionally, giant cells and Hassall's corpuscles are found. The structure varies with the number of polyhedral cells present, and different areas of the same tumor are frequently dissimilar in this respect. When polyhedral cells are numerous, the lymphocytes are scanty or absent and the structure resembles a lymphosarcoma. When scanty the structure is that of a simple hyperplasia. Occasionally, as in case 2, a characteristic lobulation is found.

The significance of thymic hyperplasia and thymomas in myasthenia gravis is still shrouded in mystery, but that some relationship does exist is shown not only by the frequency of their occurrence but by the good results reported in this disease following extirpation and irradiation of the thymus. In this connection, it is of interest that status lymphaticus resembles myasthenia gravis in the asthenia and liability to sudden death. However, the fact that abnormalities of the thymus have not been found in all cases of myasthenia gravis strongly militates against the assumption of an etiologic significance.

A possible explanation for the thymic abnormalities may lie in the suprarenal changes. In our two cases, the cortical cells were the seat of an extensive vacuolar degeneration which in areas had gone on to complete necrosis of the cells. A number of authors called attention to

¹⁵ Bell, E. T. Tumors of the Thymus in Myasthenia Gravis. *J. Nerv. & Ment. Dis.* **45**: 103, 1917.

the suprarenals in this disease Mandelbaum and Celler¹⁶ described acute congestion and a large lymphorrhage in the suprarenal cortex Marie, Bouttier and Bertrand¹⁷ found an atrophy of the suprarenal glands as a factor in the disease Alter and Osnato² noted that the chromaffin substance of the suprarenals was diminished and that the medulla was atrophic

The relationship between lesions of the suprarenal cortices and asthenia, such as occurs in Addison's disease and in chronic suprarenal insufficiency, needs no elaboration here, but that many such cases exhibit a hyperplasia of the thymus at autopsy is not so well known¹⁸ Following suprarenalectomy in the rabbit and rat, and less frequently in the dog and cat there occurs a rapid and remarkable regeneration of the thymus, even in old animals¹⁹ In infants, beginning about the second week of extra-uterine life, there occurs a spontaneous involution of the suprarenal cortex, coincident with a rapid increase in the size of the thymus²⁰ Finally, Marine assembled much evidence in support of the contention that status lymphaticus in man is dependent, in part at least, on a deficiency of some internal secretion common to both the suprarenal cortex and the gonads²¹ All these observations speak for a reciprocal relationship between the thymus and the suprarenal glands and strongly support the hypothesis that the pathologic changes in the thymus are secondary to a degenerative lesion of the suprarenal glands The cortical extract which has been found to be efficacious in Addison's disease may not be the only hormone secreted, and in analogy to the pituitary syndromes, a derangement of another hormone of the suprarenal gland may be the causative factor in myasthenia gravis

In each of the cases cited, lymphorrhages similar to those in skeletal muscles were found in the cardiac musculature This is an infrequent observation In addition to these lymphorrhages, the cardiac muscu-

16 Mandelbaum, F S, and Celler, H L A Contribution to the Pathology of Myasthenia Gravis Report of a Case with Unusual Form of Thymic Tumor, *J Exper Med* **10** 308, 1908

17 Marie, P, Bouttier, H, and Bertrand, I Etude anatomo-clinique d'un cas grave de myasthénie de Erb-Goldflam, *Ann de med* **10** 173, 1921

18 Rowntree, L G, and Snell, A M A Clinical Study of Addison's Disease, Philadelphia, W B Saunders Company, 1931

19 Marine, D, Manley, O T, and Baumann, E J The Influence of Thyroidectomy, Gonadectomy, Suprarenalectomy and Splenectomy on the Thymus Glands of Rabbits, *J Exper Med* **40** 429, 1924 Jaffe, H L The Influence of the Suprarenal Gland on the Thymus Regeneration of the Thymus Following Double Suprarenalectomy, *ibid* **40** 325, 1924 Crowe, S J, and Wislocki, G B Experimental Observations on Suprarenal Glands in Reference to Functions of Their Internal Portions, *Bull Johns Hopkins Hosp* **25** 287, 1914

20 Thomas, E Zur Histologie der Sauglingsnebenmieren, *Deutsche med Wchnschr* **37** 236, 1911

21 Marine, D Status Lymphaticus, *Arch Path* **5** 661 (April) 1928

lature showed degenerative changes. The cause of these lymphohages is obscure, an infectious or toxic agent usually having been hypothesized. Whatever the cause, findings in our cases indicate that the heart muscle is not spared.

Atrophy of the skeletal muscle, such as occurred in case 1, is also an infrequent observation.

The therapy of myasthenia gravis has been empirical, and therefore varied. Schumacher and Roth²² reported the case of a patient with myasthenia gravis associated with hyperthyroidism who benefited greatly by thymectomy. This is a radical procedure, and there is not a sufficient number of patients so treated to warrant its acceptance.

Good results by means of irradiation of the thymus were obtained by various workers.²³ Mella stated, "The myasthenic syndrome may follow on tumor of the thymus and disappear on irradiation of the thymus region." Moreover, Pierchalla⁴ advocated this form of treatment as a therapeutic test, even though thymic enlargement may not be demonstrable by roentgenograms.

To combat symptoms of suprarenal insufficiency, the extract of its cortex was employed by Marie and his co-workers²⁴ with some success. Edgeworth²⁴ tried five differently prepared suprarenal substances and found that the beneficial effects were not constant nor was muscle power improved.

Large doses of strychnine were used for this disease by Dana²⁵ with good results. Edgeworth was the first to point out the beneficial results derived from ephedrine. It will be recalled that the patient in case 1 showed definite clinical improvement with the use of this drug.

Remen²⁶ and Boothby²⁷ recently reported excellent results following the use of glycocoll. Glycocoll presumably acts in some way on the metabolism of the muscle cell. Since Wolff, Keutmann and Cobb²⁸

22 Schumacher and Roth. Thymektomie bei einem Falle von Morbus Basedowi mit Myasthenie, *Mitt a d Grenzgeb d Med u Chir* **25** 746, 1913.

23 Pierchalla,⁴ Mella,⁵ Keschner and Strauss.⁷

24 Edgeworth, Harriet. A Report of Progress on the Use of Ephedrine in a Case of Myasthenia Gravis, *J A M A* **94** 1136 (April 12) 1930.

25 Dana, C. L. Myasthenia Gravis. A Therapeutic and Clinical Study, *J A M A* **78** 261 (Jan 28) 1922.

26 Remen, L. Zur Behandlung der Myasthenia pseudoparalytica mit Glykokoll, *Deutsche med Wchnschr* **58** 889, 1932.

27 Boothby, W. M. Myasthenia Gravis. A Preliminary Report on the Effect of Treatment with Glycine, *Proc Staff Meet, Mayo Clin* **7** 557 (Sept 28) 1932. Boothby, W. M., Adams, M., Power, M. H., Edgeworth, H., Moersch, F. P., Woltman, H. N., and Wilder, R. M. Myasthenia Gravis. Second Report on the Effect of Treatment with Glycine, *ibid* **7** 737 (Dec 28) 1932.

28 Wolff, H. G., Keutmann, H., and Cobb, S. The Electromyogram in Myasthenia Gravis, *Brain* **51** 508, 1928.

showed that the fundamental defect in myasthenia gravis is peripheral to the ventral horn cells and probably in the muscle cell, such therapy is rational

SUMMARY

1 The clinical course and findings at autopsy in two cases of myasthenia gravis associated with thymomas are reported

2 Some diagnostic features of myasthenia gravis are presented: the shadow in the region of the thymus noted in roentgenograms, the diminished creatinine output in a twenty-four hour specimen of urine, the decreased sugar tolerance, the Jolly reaction, and the presence of lymphorrhages in skeletal muscle obtained through biopsy

3 The frequent association of thymomas with the myasthenic syndrome is again emphasized

4 Because of the degenerative changes found in the suprarenal cortices in our cases and in others in the literature, and because of the reciprocal relationship which apparently exists between the suprarenal cortex and the thymus, a new theory is propounded to explain the occurrence of thymomas in this disease

5 The cardiac musculature in our two cases exhibited the typical lymphorrhages which have usually been described as being present only in the skeletal muscles

6 Atrophy of the skeletal muscles, noted in one of our cases, is an infrequent observation

7 A summary of the treatment of myasthenia gravis recorded in the literature is presented

NEUROGENIC EROSIONS AND PERFORATIONS OF THE STOMACH AND ESOPHAGUS IN CEREBRAL LESIONS

REPORT OF SIX CASES

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In 1859, von Rokitsansky¹ described two forms of softening of the stomach, one a gelatinous softening said to occur in infants and a second form occurring both in children and in adults. The description in each case suggests that the processes are similar. In describing the former he said

It appears to be a metamorphosis—a softening—of the mucous membrane of the fundus, which extends to the muscular coat and the peritoneum converting them and the intervening interstitial cellular tissue into a grayish or grayish-red transparent jelly with a yellowish tinge, through which single dark brown streaks, the broken down blood vessels, are observed to pass. The softened portion of the stomach tears at the slightest touch, it dissolves between the fingers, and perhaps in rare cases these rents occur during life, but probably oftener after death, giving rise to effusion of the gastric contents into the abdominal cavity. The process is not, however, limited to the stomach, but frequently extends to the neighboring tissues, and chiefly to the muscular organs, and especially to the diaphragm. Here, too, perforation is the final result, and with it there is effusion of the gastric contents into the left pleura.

Continuing, he said of gelatinous softening: “It is frequently founded upon a demonstrable affection of the brain, principally hypertrophy or hydrocephalus.” Rokitsansky described his second form of softening as “distinguished [from gelatinous softening] by an absence of colour in the softened tissues, or rather by their colour. The parietes of the stomach are converted into a more or less saturated dark brown, or blackish pulp.” Discussing the etiology, he said: “It occurs both in children and adults as a sequela of acute affections of the brain and its membranes, and more especially of tubercular meningitis at the base of the brain.”

Read before the Chicago Neurological Society, Nov. 16, 1933

From the Departments of Neuropsychiatry and Pathology, the University of Wisconsin

1 von Rokitsansky, C. F. Pathological Anatomy, London: The Sydenham Society, 1859, p. 35

It remained for Cushing,² in his Balfour lecture, to define a clinical syndrome in which gastromalacia and ulcers of the upper portion of the gastro-intestinal tract were definitely related to disease of the interbrain. Eleven cases, illustrative of several types of lesions associated mainly with cerebral neoplasms, form the basis of his monograph. The ground had been prepared for Cushing by observations and experimental data pointing the way to this association. Cushing's theory of parasympathetic stimulation resulting in ulcer and softening has been fortified by observations made by him on human subjects into whom intraventricular injections of pharmacodynamic drugs were made.

The purpose of this article is to present a series of cases in support of Cushing's hypothesis of association with disease of the interbrain.

REPORT OF CASES

CASE 1—*Abscess of the frontal lobe with terminal meningitis, gastromalacia with perforation through the diaphragm*

G. J., a woman, aged 48, was admitted to the medical service³ on Jan. 26, 1933, appearing very ill and mentally confused. She had an infected lesion of the left cheek, which was treated by radium in February 1932, and in May 1932 she had a thyroidectomy and soon thereafter an operation on the sinus. There followed a gradual change in personality, with lethargy and despondency alternating with marked restlessness and mild mania at times, together with weakness and loss of weight.

Examination revealed emaciation, pale, dry, scaling skin, exophthalmos on the left, a left naris full of pus, two large, discrete nodules in the left posterior cervical lymph chain, changes in the base of each lung, fever and cardiac hyperactivity. A blood count revealed 4,090,000 erythrocytes, 9,100 leukocytes (86 per cent neutrophils) and hemoglobin 60 per cent.

At the neurologic examination (on February 9, after she had been in a comatose state for hours) the essential observations were edema of the disks, proptosis of the left eyeball with edema and induration of the tissues about the eyeball and firmness of the globe, flushing of the left cheek, stiff neck, weakness of all the extremities, exaggerated reflexes, bilateral Babinski reflexes, and muscular twitchings. During the examination, serous fluid flowed freely from the left nostril. Two hours later, foul pus was draining from this nostril. The temperature (axillary) was 100.4 F, the pulse rate, 112, and the respiratory rate, 36. The previous two weeks had been marked by rises in temperature to 102.6 F, the temperature at times dropping to normal and some days not rising higher than 100 F. The leukocyte count was 19,300, with 92 per cent neutrophils.

A diagnosis of abscess of the left frontal lobe and meningitis was made. A spinal puncture yielded clear fluid under increased pressure, with 70 cells and a colloidal gold curve of 00123333210. Four hours later the temperature, pulse

² Cushing, Harvey. Peptic Ulcer and the Interbrain, in *Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 175.

³ Dr. Marie Carns permitted us to use this clinical material.

rate and respiratory rate suddenly increased to 102.6 F, 140 and 44, respectively, and the blood pressure was 156 systolic and 60 diastolic. From then on the temperature (axillary) mounted to 107 F before death at 4 a. m.

Autopsy, five hours after death, revealed a dilated left pupil with bulging of the left globe. Beneath the dura of the left frontal lobe an abscess was found extending from 1.5 cm posterior to the tip of the frontal lobe to the anteroposterior portion of the left thalamus, its walls thick and covered with greenish, ragged, necrotic material. The base of the brain was covered with a thick green purulent material, and pus from a perforation of the abscess was extravasated into the sella turcica, the cribriform plate and the orbit.

Histologic examination of the interbrain (lenticular nucleus) revealed congestion, hemorrhage, areas of necrosis and perivascular lymphoid cell infiltration, with phagocytosis of hemosiderin (fig. 1). A section from the base of the brain showed

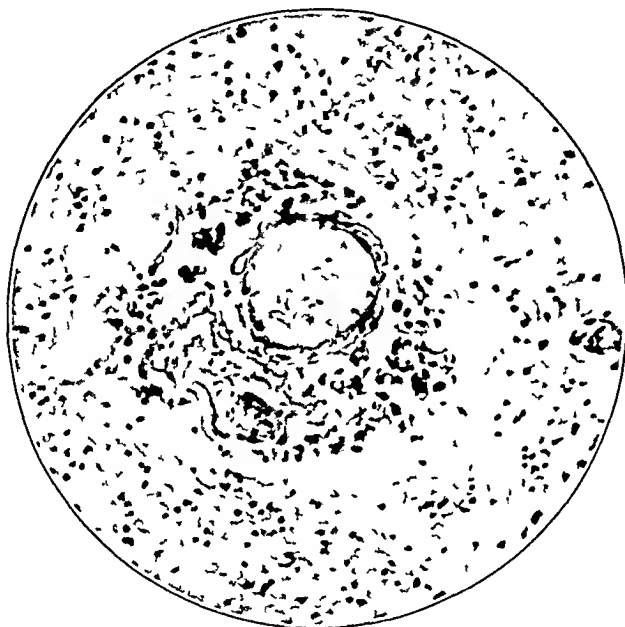


Fig. 1 (case 1) — A section from a focus in the interbrain at the periphery of the abscess, $\times 125$

acute purulent meningitis. There was an acute inflammatory process in the pituitary gland.

The abdomen contained about 300 cc of coffee-ground fluid. The stomach was dilated and the wall was extremely thin, with a perforation 6 by 2 cm near the fundus on the anterior surface. The edges of the perforation were dark green, soft and thin, with a minimal acute reaction. The diaphragm in the region of the cardiac end of the stomach was digested, with a perforation 2 by 2 cm into the thorax. Examination of the left side of the thorax revealed 250 cc of fluid similar to that found in the abdomen, with digestion of the parietal, visceral and diaphragmatic pleural surfaces. The left lung was completely atelectatic at the base, with emphysema of the upper lobe and marked emphysema of the entire right lung.

Histologic examination of the stomach revealed a partial loss of mucosa in all sections taken near the areas of perforation and a complete loss of mucosa with plasma cell and lymphoid cell infiltration around the area of perforation. Exam-

nation of the left lung revealed, in addition to the digestion of pleurae and atelectasis, early patchy areas of bronchopneumonia

CASE 2—*Acute encephalitis, with marked disturbance of the vegetative nervous system, multiple erosions of the stomach and perforation of the esophagus*

W B, a man, aged 28, was brought in in a semicomatose state on March 7, 1933 For four weeks he had complained of having a cold, but no one observed that he was ill until a few days before the onset of the acute condition, when he complained of headache and body pains and seemed to be less active and very drowsy On March 6 he was found asleep, and when aroused he continued to complain of headache and body pain

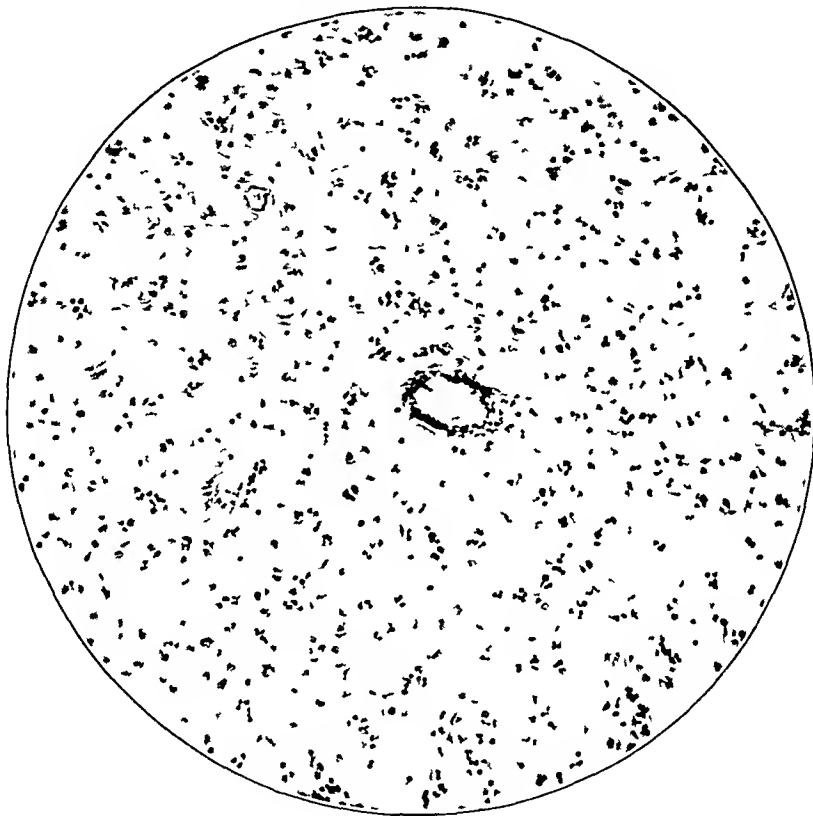


Fig 2 (case 2) —A section from the midbrain (in a case of encephalitis), showing dilated blood vessels and perivascular infiltration, $\times 50$

The patient could be aroused, but made only monosyllabic responses During the first hour in the hospital his temperature was 101 F, the pulse rate 112, and the respiratory rate, 24 The blood sugar was 160 mg per hundred cubic centimeters, and the nonprotein nitrogen, 37 mg Physical examination revealed a stiff retracted neck and back, there was no Kernig sign, but the patient's legs resisted manipulation The blood pressure was 156 systolic and 100 diastolic, and the reflexes were normal A lumbar puncture yielded clear spinal fluid under normal pressure, with 5 cells and a colloidal gold curve of 0012221000 The spinal fluid sugar was 86 mg per hundred cubic centimeters The blood sugar at the same time was 113 mg It will be noted that in an hour's time the sugar quotient dropped 47 mg without any fluid having been added to the circulation A blood count taken at the same time was as follows erythrocytes, 6,370,000, hemoglobin, 90 per cent, white cells, 11,900, polymorphonuclears, 95 per cent From this point



Fig 3 (case 2) —The stomach and esophagus showing gastromalacia and perforation of the esophagus

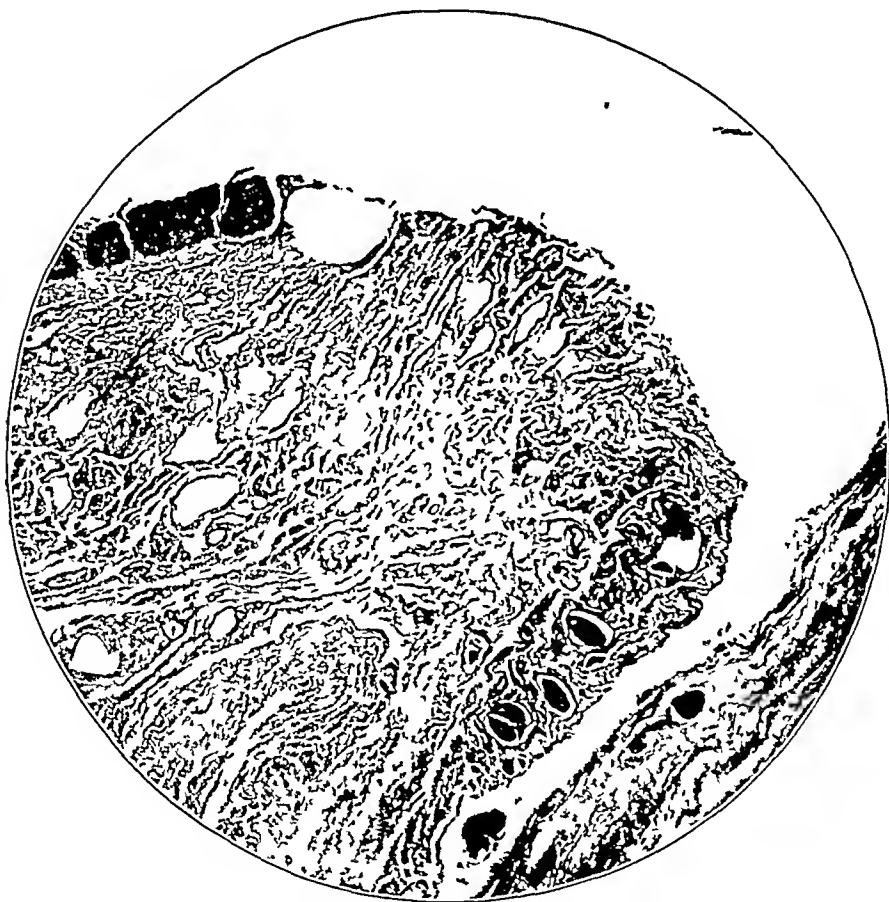


Fig 4 (case 2) —A section from the edge of the perforation of the esophagus (fig 2), $\times 30$

his temperature mounted steadily, reaching 106.4 F (axillary) on March 8. He perspired profusely at intervals. On March 8, the following observations were made: deep coma, color, livid, reactive, miotic pupils, a Kernig sign on the left, general hyporeflexia and blood pressure, 109 systolic and 70 diastolic. On March 9 a blood count revealed 7,240,000 erythrocytes, hemoglobin 100 per cent, and 26,900 leukocytes. The patient died at 5:15 a. m. on March 10. The temperature at 4 a. m. was 106.4 F. The pulse could not be counted with accuracy after midnight. The respiratory rate varied from 20 to 32 until 11:15 p. m. on March 9, when it rose to 40.

Thus, in this case the entire symptomatology—hyperpyrexia, sweating, plethoric appearance, polycythemia, hypersomnolence and disturbances of the pulse rate, respiration and blood pressure—suggests the disease process to be centered in the hypothalamic region.

Autopsy, four hours later, revealed congestion of the cerebral vessels. Microscopic examination of the cortex and the midbrain revealed widely dilated vessels with perivascular lymphocytic infiltration and slight degeneration of the ganglion cells (fig. 2). In the left pleural cavity was 500 cc. of coffee-ground fluid; after removal of the fluid it was found that the visceral, posterior parietal and diaphragmatic structures as well as the pleura over the vertebrae had been partially digested, leaving the lung with a granular hemorrhagic surface and exposing the mediastinal structures. A perforation in the esophagus (fig. 3) about 3 cm. in length was found on the left posterolateral surface just above the diaphragm; the edges of the perforation were extremely thin, soft and stained dark green. The wall of the stomach was also very thin, especially in the cardiac portion, where there were multiple erosions of the mucosa.

Histologic examination of the esophagus (fig. 4) revealed congestion and edema, with widely dilated vessels, lymphocytic and plasma cell infiltration and a complete loss of mucosa near the area of perforation with a small amount of hemorrhage in the submucosa. The stomach was extremely atrophic, there being only a few remaining undifferentiated glands with much congestion, lymphocytic infiltration and edema.

CASE 3—Tumor of the posterior fossa sexual precocity, gastromalacia, perforation of the stomach and diaphragm, localized peritonitis and acute pleurisy

L. N., a boy, aged 10, was brought to the hospital by his parents on April 18, 1933. His illness started one year before, with frontal headaches, but did not seem serious until six weeks previous to admission to the hospital. At that time he complained of double vision, the eyes appeared to protrude and the left eyeball turned inward. Two weeks later the Wassermann reaction of the blood was 2+, then 3+, while the reactions of the blood of the parents were negative. During the three weeks just previous to hospitalization, his vision became impaired, and he staggered and held his head to the left. He became restless and irritable and had difficulty in expressing himself. During the twenty-four hours before admission he had polyuria, photophobia and two convulsions.

Physical examination revealed a boy of precocious physical and sexual development. He measured 60 inches (152.4 cm.) and weighed 85 pounds (38.6 Kg.) as against 51 inches (129.5 cm.) and 61 pounds (27.7 Kg.), the normal for his age. There were fixed pupils, bilateral weakness of the sixth nerve, inability to roll the eyes upward or downward, choked disks (6 diopters), hypotonicity, increased tendon reflexes, abortive ankle clonus, a bilateral Babinski sign, resistance to flexion of the neck, generalized hyperesthesia, marked ataxia and dysmetria. The pulse rate was rapid, the temperature, normal, and the blood pressure, 124 systolic

and 94 diastolic. The Wassermann reaction of the blood was 4+. Because of the positive Wassermann reaction a cisternal puncture was made, which revealed bloody fluid under increased pressure. During the last week of life he was stuporous, with normal temperature, pulse rate and respiration until eleven hours

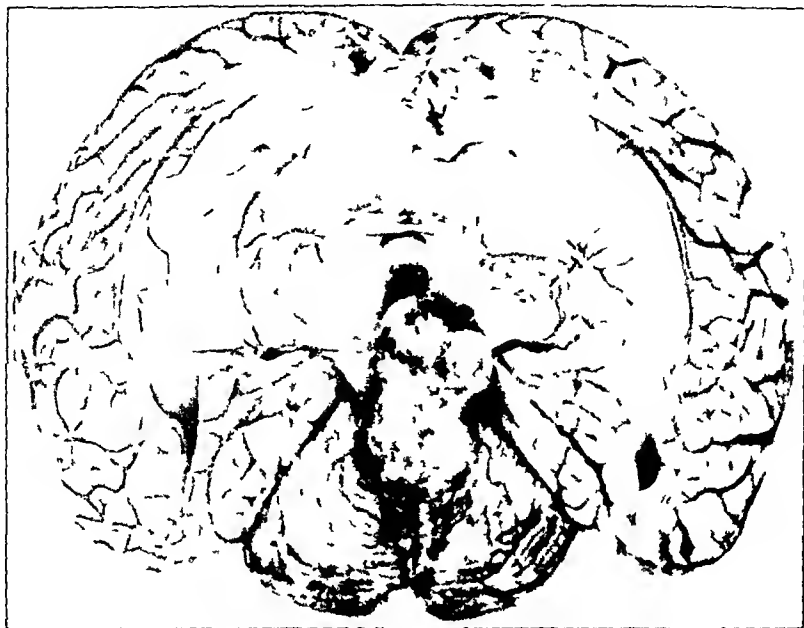


Fig 5 (case 3)—The brain, showing the tumor extending into the third ventricle



Fig 6 (case 3)—The stomach showing areas of erosion, hemorrhage and perforations

before death, when they suddenly changed—the pulse and respiratory rates increasing rapidly until death with hyperthermia (temperature, 105 F, axillary).

Autopsy, twenty-eight hours after death, revealed a large tumor arising from the superior surface of the cerebellum, measuring 7 by 3.5 by 3 cm and extending forward into a dilated third ventricle, the medial surface of the thalamus showing impressions of the tumor (fig 5), which proved to be a teratoma. In the cardiac

portion of the stomach (fig 6) were two perforations on the greater curvature, 3 by 15 cm. The surrounding wall of the stomach was thin and showed small areas of hemorrhage. The neighboring peritoneum, including the surfaces of the spleen and liver, was roughened by a granular exudate. The diaphragm above the involved portion of the stomach proved to be the location of a perforation of the diaphragm, 3 cm. in diameter, irregular in shape with softened, discolored margins. The left pleural cavity contained 500 cc. of dark brown fluid. The parietal and visceral pleura showed granular acute pleurisy and erosion.



Fig 7 (case 4) —A section from the pylorus, $\times 30$

Microscopic examination of the stomach lesion revealed inflammatory edema with diffuse submucosal hemorrhage and infiltration by lymphocytic and plasma cells.

The interest resulting from the occurrence of these three cases caused Dr. Bunting to recall the circumstance of an infant dying of hemorrhage at birth and presenting changes in the pyloric mucosa.

CASE 4—A girl, after a difficult labor, was delivered by forceps. Twitching of the extremities and spasticity of the legs led to a cisternal puncture which yielded bloody fluid. The infant died fourteen hours after birth with hyperthermia (105.8 F).

Autopsy, five hours post mortem, revealed edema with subcutaneous hemorrhage throughout the posterior portion of the scalp and several localized small subcutaneous hemorrhages in the anterior portion. The cranial cavity contained bloody fluid, both above and below the tentorium cerebelli, and there was generalized congestion of the pia-arachnoid. The anterior tip of the left temporal lobe appeared somewhat softer than the rest of the brain.

Microscopic examination of the brain revealed extreme congestion. Histologic study of a section of the stomach taken for routine examination revealed superficial antemortem necrosis of the pyloric mucosa with leukocytic infiltration (fig 7).

CASE 5—Tumor of the corpus callosum, antemortem hemorrhage, gastromalacia

F J, a man, aged 31, had been known to have a brain tumor since April 26, 1932. He had symptoms of about one year's duration, beginning with headaches,



Fig 8 (case 5)—The brain, showing extensive invasion by the tumor of the ventricles and neighboring structures

followed by jacksonian convulsions, periods of dysphasia, right facial weakness, progressive right spastic hemiplegia, choking of the optic disks (6 diopters), dysarthria and a defect of memory. A craniotomy failed to reveal the tumor in the expected location. This was followed by two courses of roentgen therapy. He was admitted to the hospital for the third time on Sept 17, 1933. A summary of the observations on that occasion follows: marked mental changes, partial motor aphasia, astereognosis, right facial weakness, apraxia of the tongue, right homonymous hemianopsia, right hemiplegia (arm more involved than the leg) and choked disks (5 diopters). A ventriculogram was made through a posterior trephination opening, revealing a midline lesion which obliterated the midportion of the lateral ventricles, flattening and depressing the roof of the third ventricle. The course of events was marked by increasing mental deterioration and stupor and a constantly elevated blood pressure, but a normal pulse rate, until the last week. During the last week he became generally rigid and took no food but was given from 600 to 1,500 cc of fluid daily. A large emesis of bright blood occurred on

November 15, and on one occasion subsequently there was an emesis of dark, thick, yellowish material. Fever (temperature not higher than 102.6 F) and an increase in the pulse rate from 130 to 180 and in the respiratory rate from 30 to 60 marked the last two days. Death occurred on November 22.

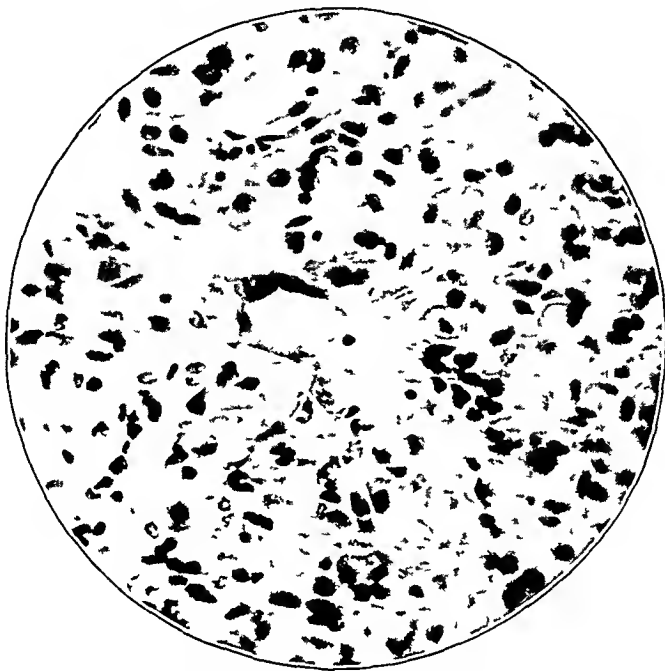


Fig 9 (case 5) —A section from the tumor shown in figure 8, $\times 280$



Fig 10 (case 5) —The stomach, showing gelatinous softening with hemorrhage and perforation (arrow)

Autopsy, thirteen hours after death, revealed an extensive brain tumor which occupied the middle fossa, extending from the inferior surface of the frontal lobes posteriorly 8 cm to involve the left internal capsule and laterally through the body of the corpus callosum into each hemisphere (invading the lateral ventricles),

measuring 9 cm in its widest portion. Microscopic examination of the thalamus (fig 9) revealed a spongioblastoma multiforme.

The stomach (figs 10 and 11) was dilated and contained 300 cc of greenish-black liquid which showed 2 degrees of free acid and 100 degrees of total acid. The cardia of the stomach was extremely thin, there remaining only a delicate transparent membrane. The thinning involved the proximal third of the stomach. A rupture 2.5 cm in diameter had occurred in the cardia anteriorly, from which a small amount of bile-stained liquid had escaped. There was a slight degree of peritoneal reaction in the vicinity of the rupture. A fairly sharp line across the fundus differentiated the very thin proximal portion from the distal thicker portion. However, the distal two thirds of the wall of the stomach was thinner than normal.



Fig 11 (case 5)—The stomach (fig 9) opened, showing perforation and hemorrhage.

Histologic examination near the rupture revealed amorphous material which contained only a few strands of muscle fiber. Other sections from the surrounding gelatinous area revealed an extreme lymphocytic infiltration and dilated blood vessels. Sections from the distal two thirds showed a similar but less intense process.

CASE 6—*Hypertensive cardiovascular disease with hemorrhage into the basal ganglia, gastromalacia, esophagomalacia and rupture.*

H S E, a traveling salesman aged 46, on January 31 was found unconscious in his car, parked at the side of a highway. He was taken to a hospital in a

4 Dr S B Pessin, pathologist, St Mary's Hospital, Madison, gave the details of this case. The pathologic specimens were presented before the staff of the Wisconsin General Hospital.

town nearby, where he died four days later without regaining consciousness. The only findings reported were fever, slow pulse rate and bloody spinal fluid. Two months before, his physician had found retinal hemorrhages and a blood pressure of 260 systolic and 130 diastolic, and had advised him not to drive an automobile.

The autopsy revealed an extensive hemorrhage involving the thalamus, the lentiform nucleus and the internal capsule, which had ruptured into the right lateral ventricle. The cerebral vessels showed much atherosclerosis, particularly those of the circle of Willis. The mucosa of the stomach was hyperemic, and there were two perforations, one 3.5 by 2.5 cm. on the anterior surface 5 cm. below the cardiac sphincter and one 3.5 cm. in diameter on the posterior wall which included 1 cm. of the esophagus. The left side of the thorax contained 1,000 cc. of thin bloody fluid, while a smaller amount was found immediately below the diaphragm on the left side. There were associated hemorrhagic pleuritis of the left lung with partial atelectasis of the lower lobe, emphysema of the right lung, localized peritonitis and perisplenitis. The observations confirming the clinical diagnosis of hypertensive (malignant) cardiovascular disease will be omitted.

COMMENT

Each of the patients was comatose for twenty-four hours or longer before death and could not have felt the pain of rupture. No patient was actively digesting food during the twenty-four hours preceding death. In none was there distention of the abdomen. In the first three cases a sudden increase in the pulse rate and respiratory rate developed several hours before death, which seems to mark the occurrence of the perforation and effusion of gastric contents into the peritoneal or pleural cavity. In case 5, there was a gastric hemorrhage a week before death.

There seems to be no question as to the antemortem nature of these observations. In all the cases histologic examination of the gastrointestinal structures showed hemorrhage and infiltration by plasma cells and leukocytes, definitely indicating active circulation and response of the tissues. The acute pleurisy and localized peritonitis in case 3 and the atelectasis and secondary emphysema and early bronchopneumonia in case 1 are indubitable evidence that the effusion of gastric contents into the left side of the thorax and abdominal cavity occurred some hours before death. If the sudden increase in the pulse rate and respiratory rate is accepted as marking the moment of rupture in case 1 it took place twelve hours before death, in case 2, six hours before, and in case 3, eight hours before, death. In case 5 a hemorrhage occurred a week before death. Large quantities of coffee-ground material, in the absence of active digestion at the time of death, and the combined acid of 100 degrees in the contents of the stomach post mortem in case 5 are evidence that there was active secretion in the stomach.

Cushing's hypothesis of a parasympathetic center in the diencephalon has received support from Beattie,⁵ working at McGill University.

⁵ Beattie, J. Relation of the Tuber Cinereum to Gastric and Cardiac Functions, *Canad. M. A. J.* **26**: 278, 1932.

This investigator exposed the third ventricle and stimulated the lateral margin of the infundibulum of his animal with an electrode. Through the open abdomen various observations were made on the viscera. The stomach showed increased peristalsis and secretion of acid. There developed increased tonus and peristaltic waves in the bladder. Hyperemic patches appeared in the mucous membrane of the lesser curvature after one-half hour of stimulation. Section of the vagus abolished these effects. Further proof that the vagus supplies the end-organ in the stomach with stimulation from the tuberal centers was derived by suturing the central end of the cut vagus with the peripheral end of a severed phrenic nerve. After waiting one hundred and eighty days for regeneration, stimulation of the tuber cinereum caused contraction of the diaphragm. Electrocardiograms made during the stimulation experiments elicited prolonged auriculoventricular conduction time.

Little⁶ and his colleagues, working in Cushing's laboratory, injected pilocarpine hydrochloride into the lateral ventricles and found that gastric ulcers developed in 94 per cent of their rabbits. Microscopic examination of these gastric lesions revealed areas of local anemia in the mucosa accompanied by surface hemorrhage and liquefaction necrosis extending as far as the muscularis.

Cushing⁷ demonstrated the effect of the intraventricular injection of solution of pituitary as well as of pilocarpine hydrochloride in man. Reactions to the two preparations were similar although solution of pituitary did not produce vomiting. The injection of 2.5 mg of pilocarpine hydrochloride resulted in a rise in blood pressure, flushing, borborvgmi, nausea, vomiting, profuse diaphoresis, a drop in temperature and finally blood-streaked vomitus. The duration of symptoms was three hours.

The interbrain is the higher center not only for the parasympathetic system but for the sympathetic system as shown by Beattie⁸ who by stimulating the posterior hypothalamus, produced secretion of epinephrine, an increase in the heart rate and diminished auriculoventricular conduction time.

It is with more than passing interest that these theories have been viewed for experience with encephalography has led to the conviction that the immediate and sometimes the more remote effects of this procedure are due to stimulation of the centers about the third ventricle, brought about by distention. Vomiting and itching are an almost con-

6 Little R. A., Bishop, C. C., and Kendall, L. G. The Production of Gastric Lesions in Rabbits by Injection of Pilocarpine into the Cerebrospinal Fluid, *J Pharmacol & Exper Therap* 45:227, 1932.

7 Cushing, - p. 67.

stant feature during the replacement of spinal fluid by air and occurs first when from 40 to 70 cc of spinal fluid has been withdrawn (from 30 to 60 cc of air replacing the fluid). This occurs at intervals throughout the procedure. Profuse perspiration and pallor are the rule. The pulse rate frequently slows to between 40 and 50 toward the end of or shortly after the procedure. The blood pressure often shows a drop, but may show an unusual rise later, after the patient has returned to bed. Blood-streaked vomitus has occurred on several occasions, and abdominal pain and desire to urinate have been noted.

In one patient, A. F., with an unconfirmed neoplasm of the middle fossa, the effects of encephalography were not evident until eight hours later, when, with the patient in marked distress, the house physician found the upper part of the abdomen distended. On inserting a stomach tube, 1,000 cc of thick, tarry material was removed, which took on the appearance of coffee-grounds toward the end of the aspiration. No evidence of further hemorrhage appeared and gastric studies a month later showed no defect in the mucosa. These effects occur in spite of the administration of 9 grains (583.2 mg) of phenobarbital sodium, which depresses the hypothalamic area, according to Cushing.⁸ It has been observed that vomiting does not occur unless the ventricles are evacuated, and that in cases of marked internal hydrocephalus few or no symptoms develop. The lateral ventricles are apparently emptied before vomiting occurs, judging from the amount of fluid which has been removed, leading to the belief that it is the emptying of the third ventricle and the distention by air which results in the disturbances in the vegetative system.

SUMMARY

Six cases of brain lesions associated with erosions and perforations of the upper part of the gastro-intestinal tract are reported.

Experimental evidence of the location of parasympathetic and sympathetic centers in the interbrain is introduced.

The effect of encephalography on these centers in the interbrain is discussed.

NOTE—Since this paper was submitted for publication two more cases have come to our attention.

H. K., a man, aged 46, had meningitis secondary to an abscess of the orbit which occurred in a degenerating tumor (adamantinoma of the left maxilla and orbit which had received roentgen therapy). When first seen his temperature was 105 F. He died in the hospital, on Sept. 19, 1934, four days after the onset, with

⁸ Cushing,² p. 219.

a temperature of 107 F. His stomach contained a large quantity of greenish-black fluid which reacted positively to the benzidine test for blood and contained 50 degrees of total acid. The mucosa of the lesser curvature was studded with numerous petechial hemorrhages. Microscopic examination of this area revealed mucosal congestion, hemorrhages and submucosal edema. The interbrain was not studied. The surface of the left hemisphere was covered with a purulent exudate.

D. T., a girl, aged 12, had symptoms of disease of the basal ganglions for four years previous to admission to the hospital on June 20, 1934. She died in a tonic convulsion on September 20, with a temperature of 105 F. During the last two hours she vomited coffee ground material which reacted positively to the benzidine test for blood. Postmortem examination was limited to the brain, in which an infiltrating neoplasm was located in the basal ganglions and upper part of the brain stem which proved to be a spongioblastoma. The gastric contents which were aspirated yielded a large quantity of material similar to that vomited before death.

ADAMS-STOKES SYNDROME WITH TRANSIENT COMPLETE HEART BLOCK OF VAGOVAGAL REFLEX ORIGIN

MECHANISM AND TREATMENT

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AND

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Complete auriculoventricular dissociation has been studied extensively by physiologists and clinicians. Through its unique physiologic mechanisms, the development of heart block often is associated with striking clinical manifestations. The dissociation of the cardiac chambers also permits an insight into otherwise concealed functions of the human heart. The observations to be reported here have yielded information which throws light on the mechanism and treatment of a rare type of heart block heretofore not completely understood.

REPORT OF A CASE

CASE 1—*History*—On July 14, 1933, F. H., a white man, aged 64, was admitted to the hospital in a stuporous state, following attempted suicide with illuminating gas. The cause of this act was despondency because of fainting spells believed to be incurable, from which he had suffered for ten years. The attacks manifested themselves in sudden dizziness or fainting lasting a minute or two and were usually precipitated by swallowing food, particularly sticky food, such as peanut butter and crackers. Sometimes only a sip of water caused an attack. The attacks developed at any time during the day, but most frequently in the morning after the first bit of food or drink was taken. The dizziness and fainting were associated with pains along the lower portion of the sternum, descending toward the stomach. At first the attacks appeared only two or three times a month, later, however they occurred two or three times daily.

The patient visited the outpatient department of the Boston City Hospital in 1926. The physical examination at that time showed no abnormality. Roentgen examination of the esophagus, however, revealed a dilatation of the lower portion, with a small diverticulum at the level of the fourth costochondral junction (fig 1). Several unsuccessful attempts were made to reproduce the attacks by swallowing Tincture of belladonna. Tincture was given in adequate doses, which decreased the number of the attacks.

When admitted to the hospital, the patient was slightly cyanotic, the face was flushed, and the respirations were slow and deep. These signs disappeared within

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twenty-four hours after recovery from the gas poisoning. The head and the shape and expansion of the thorax were normal. The cardiac dulness was 10 cm to the left of the midsternal line in the fifth costal interspace, 8 cm in the fourth and 5 cm in the third. The heart sounds were regular but rather distant. The aortic second sound was louder than the pulmonary second sound. A faint systolic murmur was heard over the apex. The cardiac rate was usually slow—48 per minute. The peripheral vessels were moderately thickened and tortuous. The pulses were equal. The arterial pressure fluctuated between 94 and 140 mm of mercury systolic and between 56 and 80 mm diastolic, the venous pressure was less than 6 cm of water. The rest of the physical examination revealed no abnormality except a slightly enlarged liver.

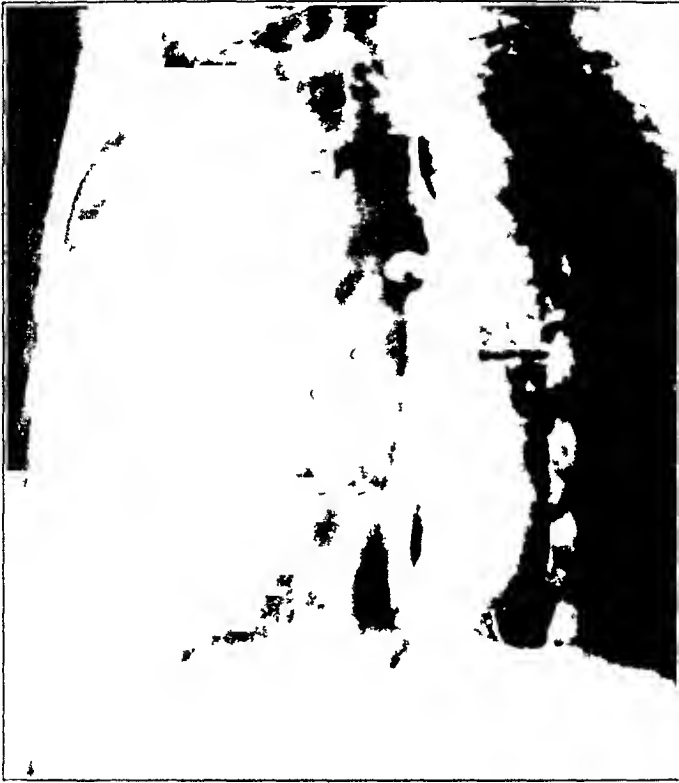


Fig 1 (case 1)—Roentgenogram of the esophagus filled with barium solution. Appearance of the diverticulum in the left oblique anterior position. The wide, rounded white area below the diverticulum is the cardiac shadow.

The red blood cell count was 4,600,000 per cubic millimeter, with a hemoglobin of 81 per cent. The white cells were normal in number and in type. The blood sugar during fasting was 94 mg., and the nonprotein nitrogen 25 mg per hundred cubic centimeters. Examination of the urine revealed no abnormalities.

The Cardiovascular System Between Attacks—As indicated, except for moderate thickening of the peripheral blood vessels, the cardiovascular system revealed no organic lesions. The patient was active and quick in locomotion without experiencing dyspnea. Repeated electrocardiograms failed to reveal any abnormality (fig 2). Sinus bradycardia was present at times. There was also a prolongation of the P-R interval up to 0.21 second on some occasions. The heart rate at rest varied from 48 to 66 per minute. The arterial blood pressure also showed variation at rest.

Spontaneous Attacks—On three occasions we had an opportunity to study the patient during attacks. Following the swallowing of food, he complained of pain over the lower third of the sternum. His face became pale, and his voice somewhat hoarse. The heart rate became slower and irregular. The venous pulsations over the neck were more rapid than the apical heart rate. The patient became listless, and in a sitting position his head drooped forward. In one or two minutes he regained consciousness, which was associated with flushing of the face and the return of normal cardiac rhythm. We had no opportunity during the spontaneous attack to obtain an electrocardiogram.

Roentgen and Fluoroscopic Observations—Repeated roentgen studies revealed that the lower portion of the esophagus was dilated, and that at the lower third there was a hook-shaped diverticulum pointing anteriorly (fig 1). The cardiac shadow and pulsations were normal. The pulmonary fields were clear except for a few small shadows interpreted as calcifications. The lesion of the esophagus was considered a traction diverticulum, resulting from previously active tuberculosis of a lymph node.

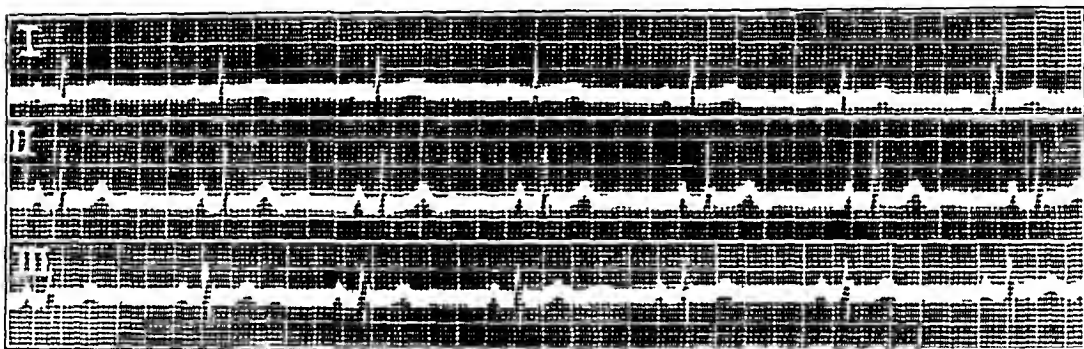


Fig 2 (case 1)—The normal electrocardiogram, leads I, II and III. The P-R interval was from 0.19 to 0.2 second.

Induction of Attacks—Following the discovery of the diverticulum of the esophagus, the question was raised as to the possible relationship between the mechanical irritation of the diverticulum and the fainting spells. In order to test the relationship, a small rubber balloon, connected with a duodenal tube and with a mercury manometer, was swallowed by the patient. Under the fluoroscope it was placed at a level corresponding to the diverticulum of the esophagus and was then distended. A pressure of from 100 to 120 mm of mercury regularly induced a sensation of distress behind the sternum, followed by dizziness, blurring of vision and temporary loss of consciousness. Release of the pressure promptly relieved the symptoms. The patient stated repeatedly that all of the manifestations associated with the induced attacks corresponded to those experienced during the spontaneous attacks.

Electrocardiograms obtained during such an observation revealed a complete auriculoventricular dissociation (figs 3, 4 and 5). Depending on the speed with which the pressure within the balloon rose, the onset of the heart block was instantaneous or delayed by a few beats. Coincidentally with the slowing of the heart rate there occurred a moderate fall in the blood pressure which varied from 28 to 40 mm. Control observations by distention above and below the level of the diverticulum failed to induce symptoms or heart block.



Fig 3 (case 1)—Electrocardiogram, lead II Continuous tracing representing control electrocardiogram and the instantaneous onset of heart block with ventricular standstill following inflation of the balloon (the vertical white line) An Adams-Stokes attack occurred

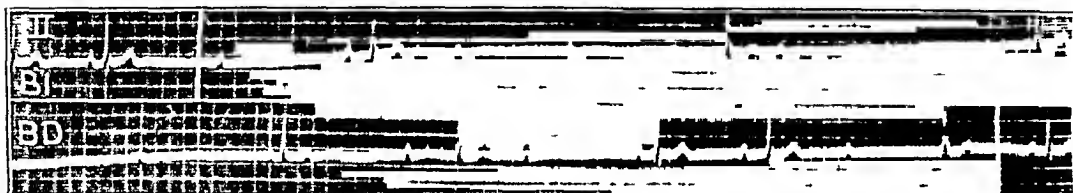


Fig 4 (case 1)—Electrocardiogram, lead II Continuous tracing representing the onset and disappearance of complete heart block with irregular ventricular rhythm The vertical white line in the control tracing (BI) indicates elevation of pressure in the balloon, and the vertical white line in the lower tracing (BD) indicates deflation of the balloon, followed by the return of sinus rhythm During the period of block two types of ventricular complexes were present An Adams-Stokes attack occurred

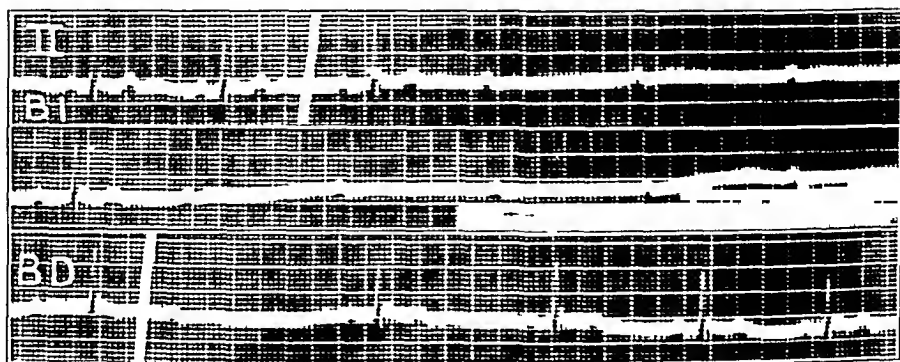


Fig 5 (case 1)—Electrocardiogram, lead II Continuous tracing representing the effect of inflation (vertical white line of BI) and of deflation (vertical white line of BD) of the balloon Following inflation of the balloon, heart block with a long period of ventricular standstill developed An Adams-Stokes attack occurred

The Effect of Drugs—The fact that the Adams-Stokes attacks and heart block could be induced with regularity by means of identical stimuli afforded an opportunity for comparing the effects of therapeutic measures used in the treatment of the Adams-Stokes syndrome occurring with the onset of heart block.

Barium chloride was administered orally at regular intervals over a period of forty-eight hours in doses of 30 mg, with a final dose of 60 mg. During the period of administration the patient suffered from four spontaneous attacks. Following this period, after 300 mg had been administered, the experiments with the balloon were performed. Severe Adams-Stokes attacks followed as usual. The administration of barium chloride was therefore continued in doses of 30 mg. A total of 150 mg was administered within the next eighteen hours, during which period the patient suffered from an additional attack. Two balloon experiments performed at the end of this period resulted in the usual symptoms and electrocardiographic findings, as shown in figure 6. The patient later took 30 mg four times a day for a period of seventeen days, and, according to his report, suffered from nine spontaneous attacks of varying severity. He believed, however, that he was somewhat improved.

Epinephrine was used in a 1:1,000 solution. One dose of 0.5 mg, administered subcutaneously, induced no appreciable change in the cardiac rate or in the

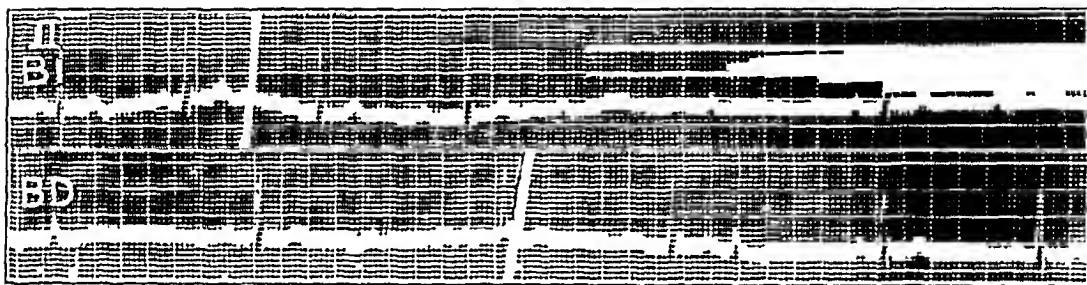


Fig 6 (case 1)—Electrocardiogram, lead II. Continuous tracing representing the lack of beneficial effect of barium chloride. Following gentle inflation of the balloon (vertical white line of BI), partial and complete block developed. An Adams-Stokes attack occurred. An ectopic auricular wave is present in the lower tracing.

arterial pressure. A similar dose was therefore given fourteen minutes later. One-half hour after the initial dose the systolic blood pressure had risen from 112 to 130 mm, and the diastolic pressure remained at 64 mm. The usual balloon experiment performed at this time failed to induce the Adams-Stokes attack. An analysis of the electrocardiograms revealed, however, that although the syncope was abolished, the increase in the intraballoon pressure induced complete dissociation (fig 7). In contrast to the irregular rhythm in the control experiments, the ventricle took up a remarkably regular ectopic rhythm at a rate only slightly less than normal.

Ephedrine sulphate in doses of 23 mg was administered at intervals of about three hours. After a total of 184 mg had been administered within twenty-four hours, during which period the patient had no attack, the balloon experiments were performed. The results of these observations were striking. Although there was no appreciable change in the cardiac rate or in the arterial pressure, stimulation of the diverticulum by means of higher balloon pressure than usual failed to induce the Adams-Stokes attack, although the electrocardiographic trac-

ings revealed instantaneous development of heart block following inflation of the balloon (fig 8). These observations were repeated with identical results. Thus ephedrine, as epinephrine, in well tolerated and relatively small amounts, abolished syncope but not the heart block. The effect of ephedrine manifested itself, as did epinephrine, in a prompt autonomic rhythm of the ventricular pacemaker, with a relatively high ventricular rate. This finding indicates that ephedrine in relatively small doses increases the excitability of the ventricles. The excitation

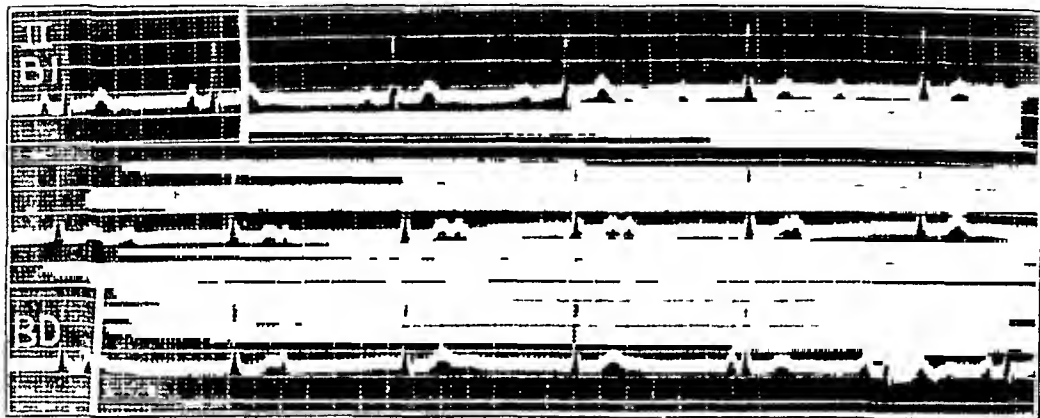


Fig 7 (case 1) —Electrocardiogram lead II. Continuous tracing representing the effect of epinephrine. Following inflation of the balloon (white vertical line of *BI*), partial, then complete, block followed. Note that after deflation of the balloon (white vertical line *BD*) a change of complete block to sinus rhythm occurred without the transition of partial block. The ventricular rhythm was remarkably regular throughout and an Adams-Stokes attack did not occur.

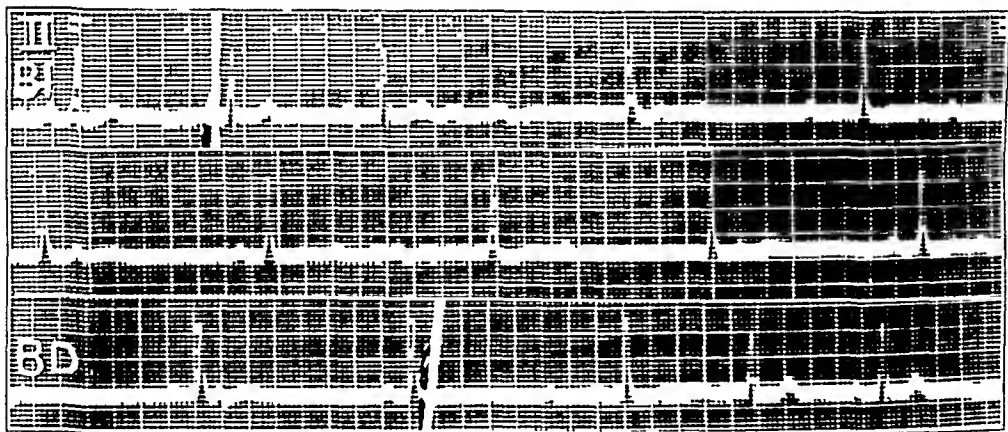


Fig 8 (case 1) —Electrocardiogram, lead II. Continuous tracing representing the effect of ephedrine. Following inflation of the balloon (vertical white line of *BI*), complete block with regular rhythm followed. Following deflation of the balloon (vertical white line of *BD*), there was a return to normal rhythm with transient partial block. An Adams-Stokes attack did not develop.

remains concealed as long as the supranodal pacemakers dominate the cardiac rhythm, but when the function of these pacemakers is inhibited, it promptly becomes manifest. During the period that the patient took ephedrine, no spontaneous attacks developed.

Atropine sulphate in a dose of 1 mg was administered subcutaneously, and sixteen minutes later, when no systemic effects were noted and the heart rate failed to show an appreciable elevation, the balloon experiment was repeated. No manifestation of an Adams-Stokes attack followed. The electrocardiographic tracing revealed partial block coinciding with the stimulation caused by the balloon (fig 9). The PR intervals were from 0.28 to 0.32 second. Twenty minutes after the administration of atropine, the balloon experiment induced no symptoms, and the electrocardiographic tracing revealed a partial block with a shorter conduction time, varying from 0.21 to 0.26 second. Twenty-one minutes after the first injection of atropine sulphate 0.5 mg more was administered, and seven minutes later inflation of the balloon failed to induce symptoms, and the electrocardiogram revealed a conduction time of from 0.17 to 0.18 second, which was shorter than that before the administration of atropine. The effect of atropine was studied in another instance with similar results. The remarkable finding in these experiments was the relatively small amount of atropine that was required to abolish the attack. In a previous study it was demonstrated that for the complete motor

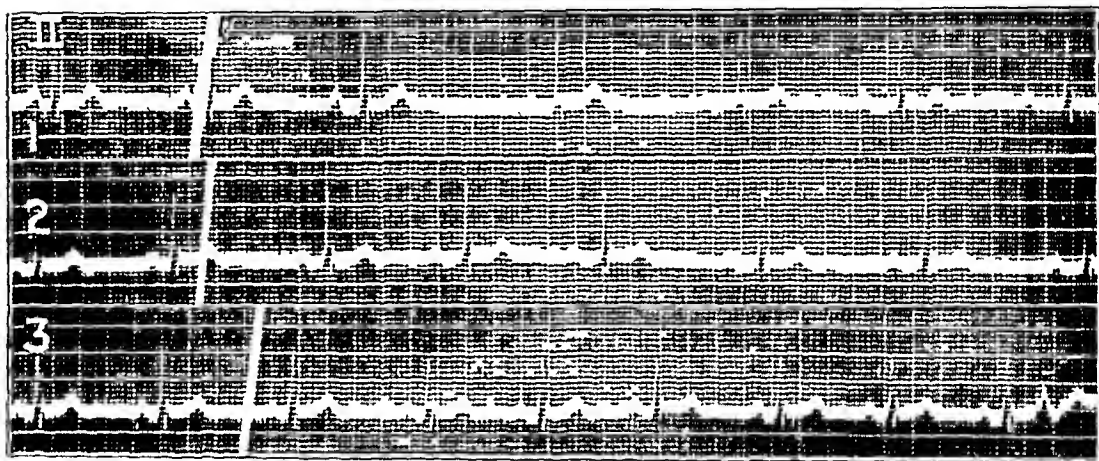


Fig 9 (case 1)—Electrocardiogram, lead II. Successive tracings indicating the effect of the administration of atropine. Tracing 1 was obtained sixteen minutes after the subcutaneous administration of 1 mg of atropine sulphate. Inflation of the balloon (vertical white line) induced prolongation of the PR conduction time and abolished the symptoms. Tracing 2 was obtained twenty minutes after the subcutaneous administration of 1 mg of atropine sulphate. The prolongation of the PR interval was less. Tracing 3 was obtained twenty-eight minutes after 1 mg and seven minutes after 0.5 mg of atropine sulphate was administered. All of the changes were abolished.

paralysis of the vagus endings in the heart it was necessary to administer from 3.5 to 5 mg of atropine.¹

Reports from the patient, following discharge from the hospital, indicated that the attacks were completely controlled by the administration of one tablet of $\frac{1}{20}$ gram (0.00054 Gm) of atropine sulphate three times a day.

The Reflex Nature of the Syndrome—The relation of the location of the diverticulum to the position of the vagus nerve chain, the precipitation of the

1 de Graff, A. C., and Weiss, Soma. Observations on the Extrinsic Nervous Control of the Auricles and Ventricles in Complete Auriculo-Ventricular Block in Man, *J. Clin. Investigation* 2:227 (Feb.) 1926.

attack by the swallowing of food and by the distention of the esophagus and the effect of atropine in abolishing the spontaneous as well as the induced attacks suggested that stimulation of the vagus nerve was responsible for the attacks. In order to ascertain whether the attacks resulted from direct local stimulation of the motor fibers or whether they developed through stimulation of the sensory fibers of the nerve trunk sending up impulses into the medullary centers, whence motor impulses are then discharged, the following studies were devised.

After control observations with the balloon experiment had indicated the induction of the Adams-Stokes syndrome and complete dissociation of the heart, first the right and then, on another day, the left vagus nerve trunk were infiltrated with procaine hydrochloride below the level of the carotid sinus. Under these conditions repetition of the balloon experiment should continue to induce heart block if the effective stimulus acts on the motor nerve, on the other hand, the stimulation of the diverticulum should fail to induce heart block, with the path of the sensory impulses blocked, if the stimulus acts on the sensory nerve. Repeated observations following the injection of procaine hydrochloride into either of the vagus nerves revealed that heart block or syncope could not be induced when the injection was made high in the neck (fig 10). These observations establish the reflex nature of the attacks. Since the afferent depressor nerve, as

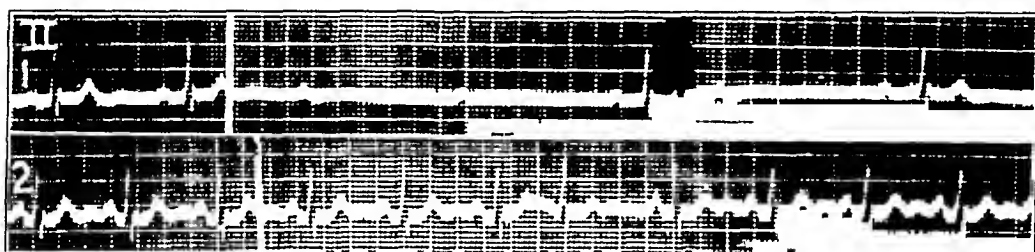


Fig 10 (case 1)—Electrocardiogram, lead II, representing the effect of procainization of the right vagus sheath in the neck. Tracing 1, the control, shows the usual development of block with an Adams-Stokes attack after inflation of the balloon. Tracing 2 was made after procainization. The heart rate increased, and the cardiac mechanism remained unaltered following inflation of the balloon.

well as the sensory nerve fibers of the vagus nerve, runs parallel to the vagus nerve, the question might be raised whether it is the afferent vagus nerve or the afferent depressor nerve that is active in the precipitation of the reflex. The fact that small doses of atropine abolished the heart block and syncope strongly suggests that the nature of this reflex was vagovagal rather than depressor-vagal.

The Effect of Stimulation of the Carotid Sinus and the Eyeballs—When the vagus was anesthetized locally in the neck, the possibility that the intercarotid nerve was also anesthetized could not be ruled out. For this reason the effect of the stimulation of the carotid sinus was tested. As indicated in figure 11, this stimulation induced a slight temporary slowing of the heart rate, a finding in accord with our contention that one abnormal cardiac or vasomotor reflex, such as the carotid sinus reflex, coexists with other vasomotor reflexes that are normal.²

² Weiss, Soma, and Baker, J. The Carotid Sinus Reflex in Health and Disease. Its Role in the Causation of Fainting and Convulsions, *Medicine* **12** 297, 1933.

It may also be contended, finally, that when the vagus trunk in the neck was paralyzed with procaine hydrochloride, the simultaneous unilateral depression of the carotid sinus may have indirectly depressed the central vagus tone, and hence the stimulation of the vagus motor fibers remained ineffective. Our actual experiences with the behavior of the carotid sinus in man do not support this contention. We have demonstrated that unilateral paralysis of the carotid sinus does not interfere with the cardio-inhibitory effect of the vagus nerve when the carotid sinus of the unanesthetized side is stimulated. Indeed, in a number of instances the intensity of the cardio-inhibitory reaction and the severity of Adams-Stokes attacks became increased.² Just as the stimulation of the carotid sinus failed to elicit abnormal response so also did pressure on each eyeball.

The Intracardiac Mechanisms of the Onset and Disappearance of Heart Block — This study afforded an unusual opportunity to analyze the changes associated with the occurrence and disappearance of heart block. We have therefore systematically analyzed particularly the conduction time (P R), the width of the ventricular complexes (Q R S) and the electrical systole (Q T). Between the attacks the only abnormal feature of the electrocardiogram was the occasional prolongation of the P R interval. The P R intervals varied between 0.17 and 0.24 second. These

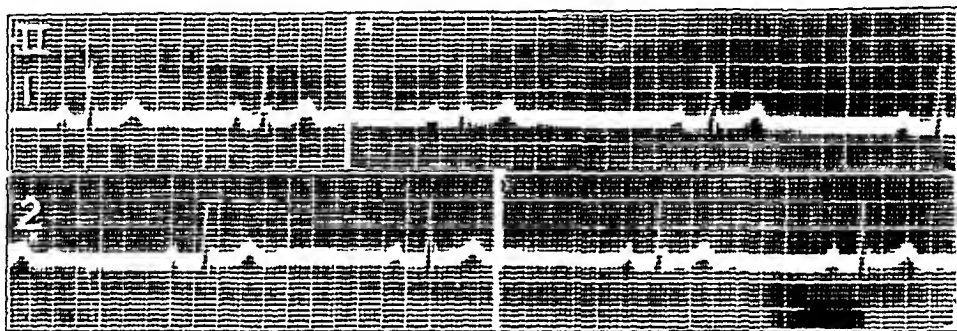


Fig 11 (case 1) —Electrocardiogram, lead II. The continuous tracing representing the effect of pressure on the right carotid sinus. The vertical white line of the upper tracing indicates the application of pressure, and the line of the lower tracing, the release. Note the slight prolongation of the P R interval and the slowing of the heart rate. No symptoms developed.

variations were apparently related to changes in sensitivity in the reflex arc. On inflation of the balloon there usually followed from two to four beats with prolonged P R intervals, after which auriculoventricular dissociation, associated with asystoles or ectopic beats, occurred. Frequently the pressure in the balloon fell temporarily, or peristaltic movements of the esophagus gradually carried the inflated balloon away from the site of the diverticulum, and hence the dissociation was interrupted by the returning domination of a higher pacemaker. The fact that the development of complete dissociation was not instantaneous but was frequently preceded by prolongation of the P R interval was the result of gradual induction of pressure in the balloon. In a few instances, when the pressure was induced suddenly, the dissociation from the normal cardiac mechanism occurred instantaneously.

An analysis of the P R intervals with progressively increased pressure in the balloon indicated that when the intervals became prolonged up to 0.32 second, auricular impulses still got through regularly. The highest interval with ventricular response was 0.35 second. With the release of pressure, partial block first

developed, the P R interval then gradually decreasing to the normal conduction. We are unable to state whether this regular occurrence was the result of the gradual release of pressure or of fatigue of the conductive system following the vagal inhibition. With the inflation of the balloon there occurred a moderate slowing of the auricles.

Analysis of the duration of the Q R S complexes, as well as of the electrical systole (Q T), revealed no definite changes during the state of dissociation.

THE EFFECT OF EPHEDRINE ON THE BLOOD FLOW IN A CASE OF COMPLETE HEART BLOCK

Observations in case 1 indicated that following the administration of ephedrine the syncope was abolished, although the complete cardiac dissociation occurred as before. In order to throw light on the possible effect of ephedrine on the blood flow, the cardiac output in a case of complete heart block was studied on seven occasions. The rate of blood flow was measured by the acetylene method of Grollman³ and by the optical method of Broemser.⁴ In therapeutic doses similar to those administered to the patient with transient heart block, ephedrine did not change the minute or the stroke volume output of the heart. The stroke volume in this case was more than double the normal volume before and after ephedrine, which is in harmony with previous experience.⁵

THE EFFECT OF DISTENTION OF THE ESOPHAGUS

The close proximity of the vagus nerves to the esophagus suggested the necessity of control observations on the effect of distention of the esophagus. This procedure was therefore carried out, in addition in two normal subjects, in two patients in whom fainting attacks were induced by carotid sinus pressure and in one patient with a diverticulum of the esophagus similar in position and extent to that in case 1, but without spontaneous fainting attacks. In none of these subjects were we able to induce any cardiac slowing or symptoms of faintness or dizziness. In a study of the mechanism of visceral referred pain Weiss and Davis⁶ also reported that distention of various portions of the

3 Grollman, A. The Determination of the Cardiac Output of Man by the Use of Acetylene, *Am J Physiol* **88** 432, 1929.

4 Broemser, P., and Ranke, O. F. Ueber die Messung des Schlagvolumens des Herzens auf unblutigem Weg. *Ztschr f Biol* **90** 467 1930. Lauber, H. Ueber arterielle Blutstromung in normalem und krankhaftem Zustand. Ergebnisse einer sphymo-manometrischen Kreislaufuntersuchung. *Ergebn d inn Med u Kinderh* **44** 678, 1932.

5 Ellis, L. B., and Weiss, Soma. Studies in Complete Heart Block. I. The Cardiac Output and the Peripheral Circulatory Mechanism, *Am J M Sc* **182** 195, 1931.

6 Weiss, Soma, and Davis, D. The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain. Skin Infiltration as a Useful Therapeutic Measure, *Am J M Sc* **176** 517, 1928.

esophagus in a group of normal subjects was never associated with dizziness or fainting or with cardiac irregularity

REPORT OF ADDITIONAL CASES WITH ADAMS-STOKES ATTACKS OF NERVOUS ORIGIN

In addition to case 1, studied extensively, we wish to report two cases in which the clinical and electrocardiographic observations demonstrate the development of Adams-Stokes attacks probably also of vagovagal reflex origin. In both cases the heart between attacks was apparently normal

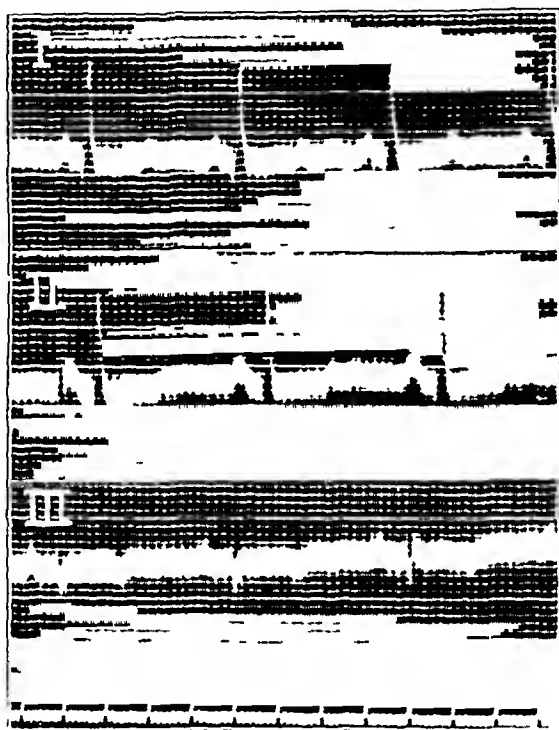


Fig. 12 (case 2)—The normal electrocardiogram, leads I, II and III

CASE 2—History—A housewife, aged 59, was observed in the Peter Bent Brigham Hospital in 1921. She had always been in good health until ten days previous to entrance to the hospital when fainting spells developed. She had fainted about thirty times. The attacks occurred in any position, and they were precipitated usually by swallowing, by something touching a "certain spot" in the throat and by dryness of the mucous membrane of the mouth. The attacks are described in the record as follows: The patient complained of a peculiar dry sensation in the left side of the throat associated with a sharp pain radiating toward the ear. The eyes were tightly compressed. The mouth closed firmly. The patient moaned. There were marked pallor of the face and distinct slowing of the pulse. Lateral oscillation of the eyeballs was noted. The patient appeared to be in a semiconscious condition during a mild attack, complete unconsciousness characterizing the more severe attacks. As the attack progressed the pupils became widely dilated, until the iris was practically invisible, and there was no

reaction to light. Diffuse perspiration broke out over the face. Tense contractions of the arm and sometimes of the legs, hands and feet occurred. The patient breathed more rapidly. Sometimes there was a conjugate deviation of the eyes up and to the left. The pupils then returned to normal size, and the patient breathed in a normal manner.

Physical Examination—The structures of the oral cavity appeared to be normal. The tonsils were not infected. There was marked pulsation of the right side of the neck. The lymph nodes were not palpated. The rest of the examination gave essentially normal results. Between the attacks the normal-sized heart was regular, with occasional extrasystole. During attacks the cardiac rate fell usually from 80 to 40, and the pulsations of the soft arteries could not be felt. The serologic tests and other examinations of the blood and urine did not yield pertinent information. The roentgen examination of the neck gave negative results. The electrocardiograms between attacks were normal. These attacks were precipitated by gagging the patient with a tongue depressor, by pressing the left eyeball

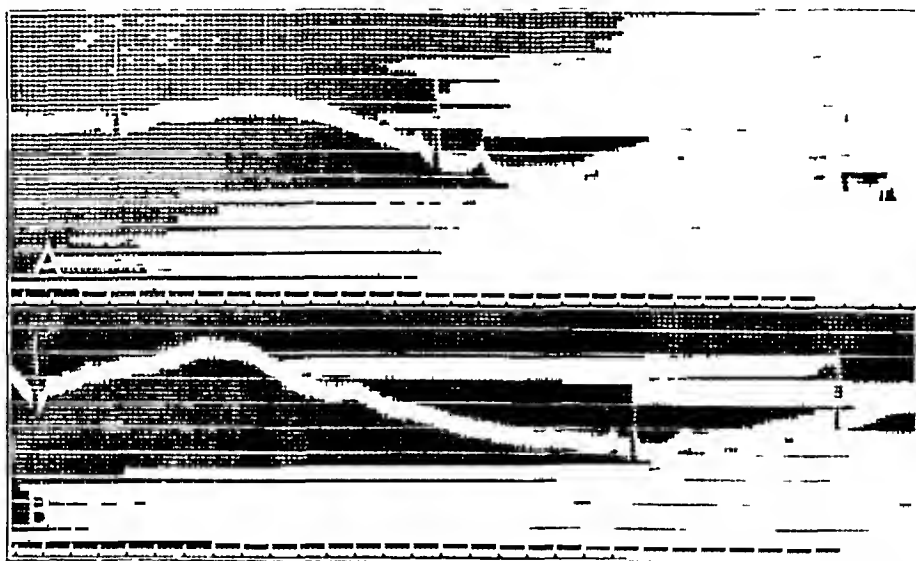


Fig. 13 (case 2) —The effect of gagging (tracing A) and of pressure over the left eyeball (tracing B). Both procedures induced marked slowing of the heart due to long sinus pauses.

and by stimulation of the vagus by pressure over the sheath. Electrocardiograms obtained during the attacks revealed markedly prolonged irregular sinus pauses up to about four seconds. No partial or complete block was present (figs. 12 and 13). Spraying of the throat with cocaine prevented the attacks, which after two weeks in the hospital showed no tendency to return. The patient was discharged improved. In April 1922, a series of similar attacks returned. Following tonsillectomy, all of the symptoms disappeared, and the patient was enjoying good health when last seen, in December 1933.

Obviously in this case, too, Adams-Stokes attacks were precipitated through a nervous mechanism in a patient who apparently had a structurally normal heart. It is of special interest that the source of attack was simple sinus slowing of the heart due to stimulation of the vagus nerve, and that the stimulation of the vagus nerve could be obtained

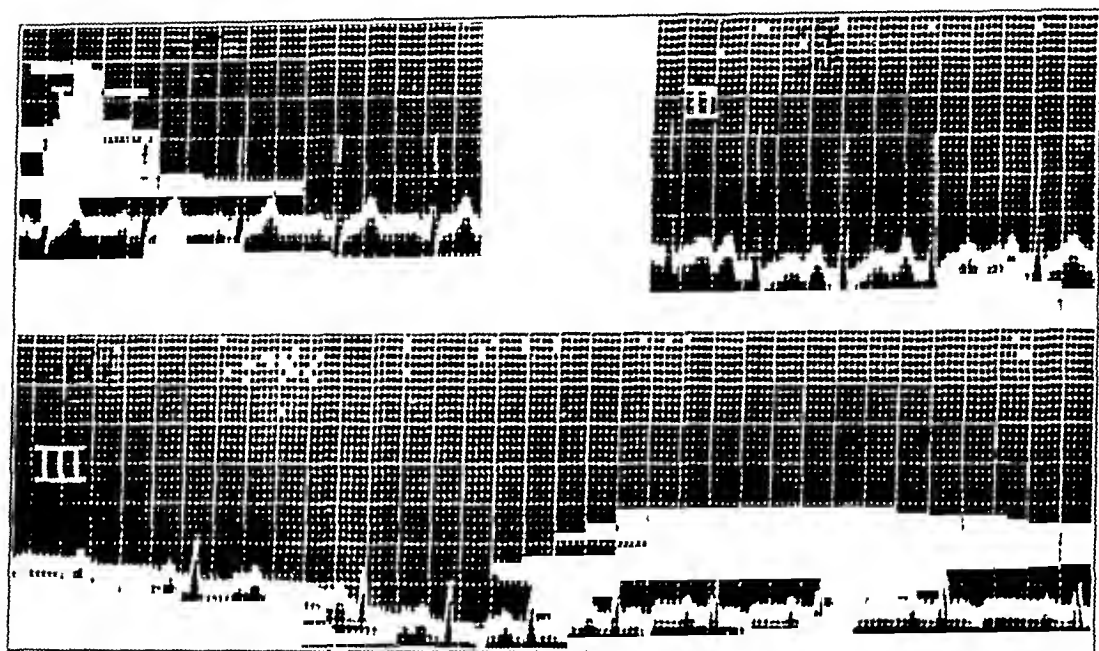


Fig 14 (case 3) —Control electrocardiograms, leads I, II, and III Lead III shows transient auriculoventricular block, caused probably by swallowing

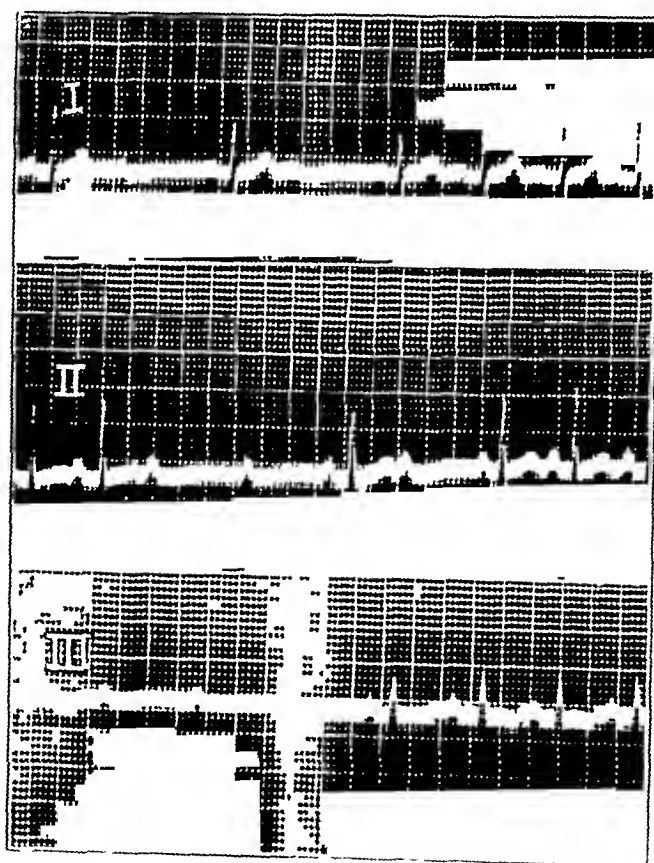


Fig 15 (case 3) —Leads I, II and III, showing the cardiac mechanism during the swallowing of food High grade auriculoventricular heart block was present

probably reflexly through stimulation of a sensory branch of the eyeball or the vagus "sheath." Thus, in this case marked vagal slowing could be induced from more than one afferent nervous channel of the parasympathetic system.

CASE 3—A woman, aged 28, was repeatedly observed by Dr. John Allen Oille of Toronto. Since the age of 2 years she had had attacks of syncope coming on particularly during meals. After 1929 the attacks appeared more frequently and at any time during the day. The patient became unconscious when playing the piano or reading or even when walking. Between attacks the results of physical examination and the electrocardiogram were normal. When the patient swallowed food the ventricle missed from one to four beats. At times, presumably when the ventricle missed more beats, she became unconscious. Electrocardiographic tracings revealed partial and complete heart block after food was swallowed (figs 14 and 15). Atropine in doses of 1 mg. abolished block.

COMMENT

Transient and Neurogenic Heart Block—The clinical aspect of case 1, as well as the relation of the Adams-Stokes attack to the esophageal diverticulum, is unique and, so far as we know, has not heretofore been reported. Transient complete block in association with the Adams-Stokes syndrome from any source is a relatively rare condition. In reporting a case of transient complete block in 1923 Carter and Dieuaide⁷ were able to collect eight additional cases previously reported. Since that time Kahler,⁸ Gager and Pardee,⁹ Carter and McEachern,¹⁰ Cheer and Tang,¹¹ and Gager¹² have reported cases, and these with our two cases, make a total of sixteen that are familiar to us. In the majority of these instances the transient heart block soon changed to permanent block, and morphologic examination of the heart revealed organic lesions in the conductive mechanism or in the coronary arteries. Thus in the majority of instances the predominant underlying lesion was structural, within the heart.

Heart block of neurogenic origin is particularly rare although in the earlier literature cases have been reported in which the source of

7 Carter, E. P., and Dieuaide, F. R. Recurrent Complete Heart Block with Normal Conduction Between Attacks, *Bull. Johns Hopkins Hosp.* **34**: 401, 1923.

8 Kahler, H. Zur Kenntnis des neurogenen Adams-Stokes, *Wien. Arch. f. inn. Med.* **7**: 207, 1923.

9 Gager, L. T., and Pardee, H. E. B. Intermittent Complete Heart-Block and Ventricular Standstill, *Am. J. M. Sc.* **169**: 656, 1925.

10 Carter, E. P., and McEachern, D. Recurrent Complete Heart-Block. Report of a Case Associated with Transient Bundle-Branch Block and Normal Conduction Between Attacks. *Bull. Johns Hopkins Hosp.* **49**: 337, 1931.

11 Cheer, S. N., and Tang, F. K. Transient Complete Heart Block with Adams-Stokes Attacks and Normal Auriculo-Ventricular Conduction Between Attacks, *China M. J.* **46**: 1081 (Nov.) 1932.

12 Gager, L. T. Intermittent Complete Heart Block, *Virginia M. Monthly* **59**: 300, 1932.

the heart block was claimed to be in the central nervous system. For the most part, however, these cases were reported previous to the discovery of the cardiac-conductive system, and no adequately thorough morphologic study of the central nervous system or of the heart was performed. Moreover, it is questionable whether the findings reported in the central nervous system had any causative relationship to the heart block.

The theory that the nervous system, the vagus nerve in particular, is responsible for the Adams-Stokes syndrome is relatively old. It was first suggested in 1872 by Charcot¹³ following the classic demonstration of the inhibitory effect of the vagus on the heart by the celebrated Weber brothers in 1850. Previous to the discovery of the conductive system, such lesions as softening of the cerebellar peduncle or the vagus centers, compression of the medulla oblongata or the pons and intracranial vascular varicosities were held responsible for the symptoms.¹⁴ With the discovery of the conductive system of the heart in the beginning of the present century, however, primary structural or functional changes within the system were held to be responsible for the Adams-Stokes syndrome and for complete heart block. As organic lesions of the conductive system were demonstrated in the majority of instances, and, contrariwise, as direct clinical or experimental evidence for the neurogenic origin of heart block was lacking, the theory of the primary neurogenic etiology of the Adams-Stokes syndrome with heart block was practically discarded.

Only a few cases of heart block in which there was adequate evidence of nervous origin have been reported. In the cases of Hay,¹⁵ Lutenbacher,¹⁶ Gallemaerts,¹⁷ Starling¹⁸ and Kahler,⁸ the precipitating rôle of the vagus nerve was suggestive, nevertheless, the primary rôle obvious of organic lesions or of nutritional disturbances of the heart is definite. The case reported by Flaum and Klima in 1932¹⁴ is one of the best examples of the Adams-Stokes syndrome of nervous origin. In this instance, a patient, aged 63, previously in good health, had severe pain in the left side of the throat and neck after swallowing. On some occasions the pain was associated with syncope of from one to two

13 Charcot, J. M. *Leçons sur les maladies du système nerveux faites à la Salpêtrière*, Paris, A. Delahaye, 1872-1873.

14 Flaum, E., and Klima, R. *Zur neurogenen Form des Adams-Stokesschen Symptomenkomplexes*, *Wien Arch f. inn. Med.* **23** 223, 1932. Kahler.⁸

15 Hay, J. *Bradycardia and Cardiac Arrhythmia Produced by Depression of Certain of the Functions of the Heart*, *Lancet* **1** 139, 1906.

16 Lutenbacher, R. *Bradycardie orthostatique. Intermittence de conduction du faisceau de His*, *Arch. d. mal. du cœur* **12** 145, 1919.

17 Gallemaerts, V. *Dissociation auriculo-ventriculaire provoquée par l'orthostasme (bradycardie orthostatique)*, *Arch. d. mal. du cœur* **16** 332, 1923.

18 Starling, H. J. *Heart Block Influenced by the Vagus*, *Heart* **8** 31, 1921.

minutes in duration. Although the laryngoscopic examination gave negative results, it was found that pressure on the sinus piriformis precipitated syncope with pain identical to that which had occurred spontaneously. The authors concluded that the cardiac slowing was precipitated by the stimulation of the superior laryngeal nerve through one of the sensory nerves of the larynx. This belief was confirmed by the fact that anesthetization of the larynx abolished the attacks. Electrocardiographic studies revealed that the cardiac slowing was due to sino-auricular block. Thus, in this case, stimulation of a sensitive afferent vagus branch resulted in bradycardia with sino-auricular block. The similarity between this case and case 2 of our group is striking.

Gluch¹⁹ reported the occurrence of the Adams-Stokes syndrome resulting from sinus arrhythmia with marked bradycardia in a case of bronchiogenic sarcoma causing paralysis of the recurrent laryngeal branch of the left vagus. Irritation of the vagus nerve by the tumor must have occurred, and the relation of the tumor to the vagus nerve was somewhat similar to that of the diverticulum in the case studied by us. In a previous communication we also recorded instances in which transient complete heart block with the Adams-Stokes syndrome was induced through stimulation of the carotid sinus.² In these cases complete heart block resulted from a reflex stimulation. The afferent portion of this reflex reached the medullary centers through the inter-carotid nerve, motor impulses then being discharged from the vagus center to the heart. One of us (Dr Weiss)²⁰ gave evidence that cardiac slowing induced by digitalis is due in part to a vagovagal reflex rather than to local stimulation of the vagus endings. These clinical and experimental experiences were the basis for the belief that "motor stimulation of the vagus depends, at least in the majority of instances on reflex stimulation."² The demonstration (case 1) of the fact that even in direct mechanical stimulation of the vagus nerve sensory rather than motor impulses are set up further substantiates this belief. Recent experimental evidence for the reflex nature of vagal stimulation in animals is not lacking.²¹ Thus Adams-Stokes syndrome caused by bradycardia is at times not only neurogenic but reflex in origin. The nature of the bradycardia can be simple sinus arrhythmia, sino-auricular block or complete auriculoventricular block.

19 Gluch, B. Elektrokardiographische Beobachtungen bei dem Morgagni-Adams-Stokes'schen Symptom-Komplex, *Ztschr f Kreislaufforsch* **24** 561 (Sept 15) 1932

20 Weiss, Soma. The Effects of the Digitalis Bodies on the Nervous System. An Analysis of the Mechanism of Cardiac Slowing, Nausea, and Vomiting, Psychosis, and Visual Disturbance Following Digitalis Therapy, *M Clin North America* **15** 963, 1932

21 Hevmans, C. Le sinus carotidien et les autres zones vasosensibles reflexogenes, London, H. K. Lewis & Co., 1929

The spontaneous fluctuations in the basal cardiac rate, in the auriculo-ventricular conduction time and in the arterial blood pressure in our case suggest that the parasympathetic tone varied from day to day, depending presumably on the local process within the diverticulum and on the general bodily state of the patient. Such daily variations in the vagal tonus offer an explanation as to why the spontaneous attacks of syncope, as well as the attacks induced experimentally, developed more easily at one time than at another.

In certain cases with primary organic disease within the heart,²² a superimposed increased vagal tonus has played a precipitating rôle in the development of the complete auriculoventricular dissociation. In other instances, with only incomplete severance of the conductive system by local organic lesions, a combination of added insufficient coronary circulation and depression of the remaining functioning conductive system by bacterial toxins or drugs has played a precipitating rôle. Thus multiple causes rather than a single cause are often responsible for the development of the transient auriculoventricular dissociation. The results of the study of our case nevertheless indicate that the primary and dominating factor was sensory irritation of vagal afferent fibers. No evidence for the existence of secondary factors was available. The remarkable fact that the attacks have recurred over a period of ten years without change in character and with only slight increase in tendency also supports this contention. Thus, the appearance of the Adams-Stokes syndrome does not always, as is generally believed, offer a bad prognosis. It does so usually because in the vast majority of instances the syndrome is an indication of severe organic heart disease.

The Mechanism of Syncope—The onset of syncope occurred in from fifteen to thirty seconds after the induction of heart block described here. Obviously the duration of the asystole and the ensuing cerebral ischemia were determining factors. In several of the attacks it was noted, however, that the arterial pressure during the syncopal attack was lowered only slightly, while during the onset of heart block after the administration of ephedrine, when the cardiac rhythm was regular and no syncope developed, the degree of fall in the arterial pressure was greater. It appears, then, that a sudden stoppage or slowing of the blood flow, even with maintained blood pressure, was a more active factor in the precipitation of an Adams-Stokes attack than was a slow, regular rhythm or fall in arterial pressure. The experience of sudden dizziness and sensation of faintness, associated with the occurrence of a single premature beat, also supports this contention. In a previous study of the cerebral circulation in fainting and convulsions following stimulation of the carotid sinus, we brought forward evidence showing that in the precipitation of cerebral symptoms, the rate of

change from the normal state to an ischemic state rather than the absolute degree of ischemia plays a dominant rôle - Obviously, in the presence of an inelastic and sclerotic vascular system, the same degree of asystole will result in a greater degree of cerebral ischemia. Through excitation of vascular reflexes, an active constriction or dilatation of the cerebral blood vessels may also occur which can further accentuate or diminish, respectively, the degree of ischemia. It has also been shown that vasomotor and circulatory changes associated with changes in the bodily posture also have an important bearing on the rate of development of cerebral ischemia -

Often it is difficult to differentiate between the ischemia resulting from the cardiac irregularity and that resulting from the simultaneous activity of other vasomotor reflexes. It is known, for example, that the arterial blood pressure and the vasomotor state may show considerable periodic fluctuation in the different stages of Cheyne-Stokes breathing. Syncope occurs at the apneic stage even without appreciable slowing of the heart. In other instances, however, the apneic stage is associated with marked slowing of the heart rate as a result of simultaneous sinus bradycardia or of temporary partial or complete block due to a rhythmically shifting pacemaker. In such instances it is difficult to evaluate the relative rôles of the primary vasomotor changes and the cardiac ischemia. That in some of these instances the vasomotor rather than the cardio-inhibitory factor predominates is shown by the fact that the appearance of early symptoms of Adams-Stokes attacks in such cases may precede the onset of cardiac slowing.²³ It is the various combinations of these factors that result in marked differences in the time of onset of syncope. Thus, ventricular standstill varying from six to sixty-seven seconds in duration has been reported to occur before the onset of convulsive movements.²⁴

In a study of the interaction between the emotional states and the cardiovascular system, it was pointed out that clinical evidence suggests that certain sensations such as anxiety and nervousness have their origin in the heart and particularly in coronary disease.¹ Other clinical manifestations also indicate that certain features of the Adams-Stokes syndrome may be due to sudden disturbances of some at present unrecognized nervous connection between the heart and the central nervous system. Thus in the precipitation of syncope of the Adams-Stokes type, in addition to the factor of general ischemia, other factors particularly reflexes play an important rôle.

23 Weiss, Soma. Unpublished observations.

24 Weiss, Soma. The Interaction Between Emotional States and the Cardiovascular System in Health and in Disease, Emanuel Libman Anniversary Volume New York, International Press 1932, vol 3, p 1181.

The Comparative Value of Drugs—A comparison of the efficacy of the therapeutic agents used shows that while barium chloride was without effect or was only slightly beneficial, ephedrine, epinephrine and atropine abolished the Adams-Stokes attacks. Atropine prevented the block, ephedrine and epinephrine abolished the irregular periods of asystole attending the onset of block but did not prevent the block. The beneficial effect of ephedrine in small doses is particularly significant, as this drug can be taken orally without unpleasant secondary effect. Our observations suggest that ephedrine, when administered in doses which do not raise the rate of sinus rhythm, increases the excitability of the ventricles. Contrary to experience in other diseases, in the type of Adams-Stokes attack described, ephedrine can be used more advantageously than epinephrine. The use of ephedrine in an Adams-Stokes attack has been advocated in recent years,²⁵ barium chloride on the other hand, after a claim for its beneficial effect²⁶ has been found repeatedly ineffective²⁷. We found that it was ineffective in four cases of heart block with Adams-Stokes attack.²³ We did not use digitalis in the study, because it increases the vagal tone, and hence it was feared that it might increase the severity of the spontaneous and induced attacks.

Our experiences with these drugs are not necessarily applicable to the Adams-Stokes attacks in patients with permanent block. In such instances the prevention of a low cardiac rate with resulting decreased blood flow is the chief therapeutic aim. As the vagus control over the ventricles is to a large extent ineffective in the presence of complete permanent block, atropine usually is of slight or no beneficial effect, and digitalis is of questionable usefulness. Thus the medication of choice in these cases, too, is ephedrine and epinephrine.

25 Hollingsworth, M. Ephedrin in Adams-Stokes Syndrome, *California & West Med* **26** 802, 1927. Stecher, R. M. A Note on Stokes-Adams Disease Treated with Ephedrin, *Am Heart J* **3** 567 (June) 1928. Parade, G. W., and Voit, K. Zur Adrenalin- und Ephetoninbehandlung der Adams-Stokesschen Krankheit, *Deutsche med Wchnschr* **55** 179, 1929. Wood, J. E., Jr. Treatment of Adams-Stokes' Syndrome with Especial Reference to the Use of Ephedrine, *South M J* **25** 927, 1932. Roberts, L. J., and Taber, T. H. Ephedrine in the Treatment of Adams-Stokes Syndrome. Report of Case, *U S Nav M Bull* **31** 27, 1933.

26 Cohn, A. E., and Levine, S. A. The Beneficial Effects of Barium Chlorid on Adams-Stokes Disease. Report of Three Cases, *Arch Int Med* **36** 1 (July) 1925.

27 Heard, J. D., Marshall, W. R., and Adams, F. S. Heart-Block with Convulsive Syncope. Case Report and Pathological Findings in a Patient Unsuccessfully Treated with Barium Chloride, *Am Heart J* **2** 562, 1926-1927. Parsonnet, A. F., and Hyman, A. S. Barium Chlorid in the Stokes-Adams Syndrome of Complete Heart Block. Negative Results in Eight Cases, *Am J M Sc* **180** 356, 1930.

SUMMARY AND CONCLUSIONS

1 This study centers around observations on a patient who for ten years suffered from attacks of fainting precipitated usually by the swallowing of food. The patient had a traction diverticulum of the esophagus, distention of which with the aid of a rubber balloon promptly induced auriculoventricular dissociation of the heart and syncope. The release of pressure in the balloon was associated with a prompt return of normal sinus rhythm and the disappearance of symptoms.

2 Distention of the esophagus of normal subjects and of patients with syncope due to hyperactivity of the carotid sinus failed to induce fainting or change in the cardiac rhythm.

3 Barium chloride failed, not only to influence the severity and the frequency of syncope, but also to prevent the development of heart block. Epinephrine and ephedrine in small doses, which induced no change in the arterial pressure and only slight elevation in the heart rate, abolished all of the symptoms although pressure on the diverticulum continued to induce complete heart block. Following the administration of epinephrine and ephedrine the onset of idioventricular rhythm, in contrast to the control observations, was associated with remarkably regular rhythm as a result of increased excitability of the ventricles. Atropine in doses which produced only slight depression of the vagal motor endings abolished the symptoms as well as the heart block. Paralysis of either of the vagus sheaths in the neck with procaine hydrochloride also abolished the fainting and the block.

4 The Adams-Stokes attack in this case was induced by heart block precipitated by a vagovagal reflex. The source of the reflex was irritation of the sensory endings of the vagi by the diverticulum.

5 The intracardiac mechanism active at the onset and the disappearance of heart block of reflex origin are described.

6 The cardiac output and other aspects of the hemodynamics in a case of complete heart block were studied with the acetylene and optical methods. Ephedrine failed to induce a significant change in the blood flow.

7 The relative role of organic cardiac lesions and of neurogenic factors in the precipitation of Adams-Stokes attacks with heart block is discussed, and the simultaneous presence of multiple etiologic factors is stressed.

8 In addition to the three cases of vagovagal reflex origin presented here, and to those due to hyperactive carotid sinus, previously reported, there are only two cases of the Adams-Stokes syndrome familiar to us in which changes in the cardiac rhythm were primarily of vagal origin.

In this group with neurogenic Adams-Stokes attacks the precipitating cardiac mechanisms were sinus pauses, sino-auricular block, partial and complete block and total cardiac standstill

9 It has been demonstrated that abnormal hyperactivity of the vagovagal reflex can be associated with a normal state of other reflexes of the same type

10 In the precipitation of Adams-Stokes attack, cerebral ischemia due to decreased cardiac output is only one factor. The rôle of other factors, particularly of vasomotor reflexes, is emphasized

Dr Henry A. Christian and Dr Samuel A. Levine permitted us to include in this study case 2, observed in the Peter Bent Brigham Hospital, and Dr John Allen Oille permitted us to describe case 3

THE HEART AND GREAT VESSELS IN COMBINED SYPHILITIC AND RHEUMATIC INFECTION

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Two diseases the cause of cardiac dysfunction syphilis and rheumatic fever, are seldom reported as associated in studies of these two diseases Cowan and Rennie,¹ in a study of one hundred and four patients suffering from disease of the aortic valves, found definite rheumatic disease of the mitral valve in 31 per cent of those with syphilis of the heart Cotton² found among fifty patients with aortic insufficiency with an average age of 31 years that 2 per cent gave a history of syphilis Fordyce reported nine cases of children with rheumatic heart disease with a severe course in whom asymptomatic congenital syphilis was discovered The contribution of Von Glahn and Wilshusen⁴ included the pathologic study of two cases of recent rheumatic myocarditis superimposed on syphilitic aortitis In the Joseph Sailer Cardiac Clinic of the Philadelphia General Hospital, four cases of frank rheumatic heart disease with a superimposed infection of syphilis were found in a series of nine hundred and twenty-three patients In these four, the rheumatic infection was clinically quiescent and remained so through the entire course of antisyphilitic therapy In the fourth case, one of neurosyphilis with rheumatic mitral disease the spinal fluid was persistently resistant to treatment

In one thousand and thirty-one autopsies performed at the City Hospital between Jan 1 1927, and Oct 1 1931 seventy-one (exclusive of aneurysm) were on syphilitic patients with clinical heart disease Of this group, eight were found with rheumatic heart disease Six hearts of this group were available for study and form the basis for this report

Read before the Section on General Medicine of the College of Physicians, Philadelphia, Feb 27, 1933

From the Department of Pathology and the Electrocardiographic Laboratory of the Medical Services, City Hospital, Welfare Island, Department of Hospitals

1 Cowan, J., and Rennie, J K Syphilis of the Heart Brit M J **2** 184, 1921

2 Cotton, T F Observations of Aortic Disease in Soldiers, Lancet **2** 470, 1919

3 Fordyce, A D Undetected Syphilis in Rheumatic Infection in Children Brit M J **1** 530, 1930

4 Von Glahn, W C and Wilshusen, H J Syphilitic Aortitis and Acute Rheumatic Myocarditis Proc New York Path Soc **24** 71, 1924

REPORT OF CASES

CASE 1—S P, a Negress, 16 years old, a schoolgirl, was admitted to the City Hospital on May 27, 1927, because of sore throat, painful joints, a rash on the body and dyspnea. At the age of 11, she had chorea, at 13, pertussis. She had always been subject to sore throat. Nine months previously, she had an attack of poly-

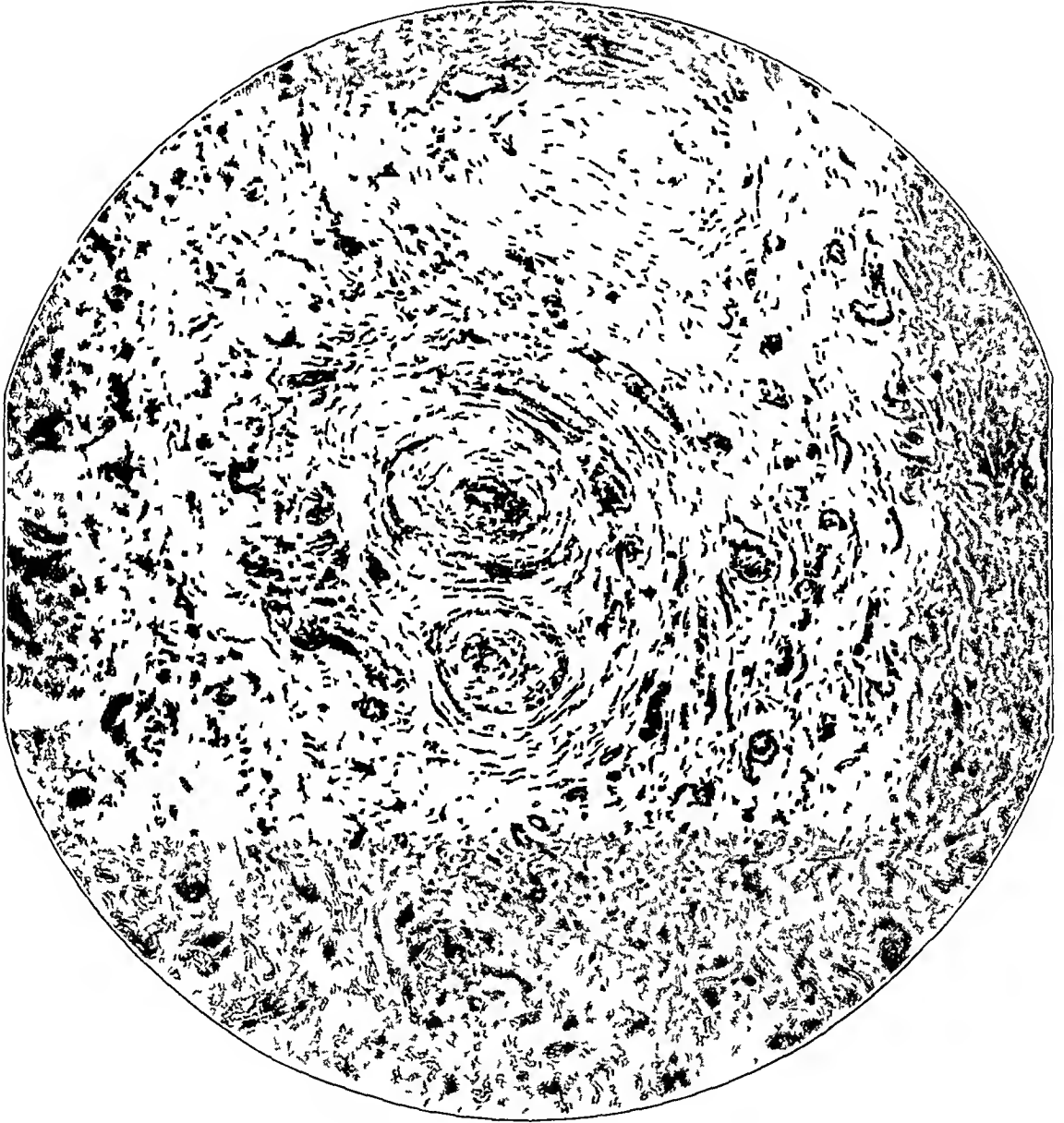


Fig 1—Endarteritis of the vasa vasorum in the commissural region, a lesion found in five of the cases

arthritis. Some weeks later, during an examination previous to tonsillectomy, a cardiac lesion was discovered. Early in 1927, there was cardiac decompensation, but recovery was prompt. Shortly afterward, following exposure, she contracted a genital sore which did not heal.

On physical examination the patient was moderately orthopneic. The pupils were slightly unequal, but responded to light and in accommodation. There were

a generalized rash on the body, mucous patches on the mouth, a chancre on the left labium, condylomas and general adenopathy. The precordium bulged. Percussion revealed the heart to be greatly enlarged. There was a thrill with a loud blowing to-and-fro murmur over the precordium. Thrill and pistol shot sounds were present over the carotid, brachial and femoral arteries. There was a booming systolic murmur over the aortic area, the aortic second sound was absent. The liver was palpable. The blood pressure was 120 systolic and 30 diastolic. No type of cardiac pain was present. A Wassermann test of the blood showed a reaction of 4 plus. Under treatment with bismuth, salicylates and rest she improved and compensation was restored. She was discharged improved on July 10, and was referred to the clinic for further treatment.

The second admission was three days, later, with decompensation. With the exception of syphilitic lesions of the skin and mucous membranes, the condition was the same as previously. The pupils were normal. The response to therapy was slower, and compensation was not restored until October, when the mother insisted on taking her home against advice.

The third admission was on Jan 23, 1928. Compensation continued until December, when decompensation recurred. She was extremely dyspneic, orthopneic and had generalized edema. The heart was regular, with a rate of 140. There were a presystolic thrill, shock and a harsh to-and-fro murmur at the apex. There were a pericardial friction rub, visible pulsation of the vessels of the neck and a thrill over the carotid arteries. Ascites was present. The blood pressure was 158 systolic and 35 diastolic. The white blood cell count was 13,000, with 82 per cent polymorphonuclears. The urine contained large amounts of albumin and many casts. The Wassermann reaction was negative. The temperature was from 98 to 100 F, the pulse rate from 112 to 140 and the respiratory rate from 28 to 46.

The roentgen examination showed marked enlargement of the left ventricle, enlargement of the right ventricle, marked enlargement of the left auricle (showing as a double shadow on the right side)⁵ and enlargement of the auricle. The aorta was not dilated.

The electrocardiogram showed normal sinus rhythm, simple tachycardia, prolonged auriculoventricular conduction time and no axis deviation. There was slurring of the ventricular complexes.

Death occurred three days after the third admission.

The clinical diagnosis was rheumatic pancarditis, mitral stenosis and insufficiency, and aortic stenosis and insufficiency. The anatomic diagnosis was rheumatic pancarditis, acute interstitial myocarditis, recent pulmonary infarction, general chronic passive congestion, anasarca, and syphilis of the aorta.

The case was predominantly one of rheumatic fever with a typical history, physical findings and clinical course, with first decompensation preceding syphilitic infection, poorly sustained compensation despite therapy and death from congestive failure, complicated by superimposed acute myocardial infection of undetermined etiology.

CASE 2—S. F., a Puerto Rican woman, aged 26, was admitted to a hospital on Jan 25, 1928, because of dyspnea, precordial pain and edema of the ankles. She had always been subject to sore throat. She had never been pregnant. She was well until one year previously, when she had an attack of acute polyarthritides which confined her to bed for six months. In October 1927 she first suffered precordial

⁵ Nichols, C. F., and Ostrum, H. W. Unusual Dilatation of the Left Auricle, *Am Heart J* 8 205, 1932.

pain and swelling of the feet. She was in a hospital for five weeks and was discharged improved. Early in January 1929 the same symptoms recurred, and she entered a hospital. Physical examination showed a marked precordial heaving impulse, the apex beat in the sixth interspace in the midaxillary line and the right border 3 cm. to the right of the midsternal line. There was a short presystolic crescendo murmur and a loud systolic murmur at the apex. The pulmonic second sound was greater than the aortic second sound. The liver was enlarged, extending three fingerbreadths below the costal margin, and was tender. The Wassermann reaction was 4 plus.



Fig. 2 (case 2)—Posterior view of the heart. The tricuspid valve (*B*) and the mitral valve (*C*) have stenotic rheumatic lesions. The superior cava (*A*) is thrombosed, the thrombus extending down into the auricle. The probe indicates the mouth of the vessel.

On entering the City Hospital, there was a slight presystolic thrill at the apex and diastolic shock. There was a systolic murmur at the aortic area. There were frequent extrasystoles. The blood pressure was 130 systolic and 70 diastolic. The liver was just palpable. The Wassermann reaction was 4 plus.

On February 6, she complained of chills, fever, sore throat and pains in the neck and chest. The temperature was 102 F, the pulse rate 120 and the respiratory rate 32. The throat was red and injected, and the glands on both sides of the

neck were painful. The observations on the heart were unchanged. The liver was larger and tender. The white blood cell count was 15,000, with 85 per cent polymorphonuclears. By February 10 she had improved, and the temperature had returned to normal. It was not until some days later that the size of the liver decreased and the tenderness disappeared. Ten cubic centimeters of tincture of digitalis was administered from January 26 to January 31.

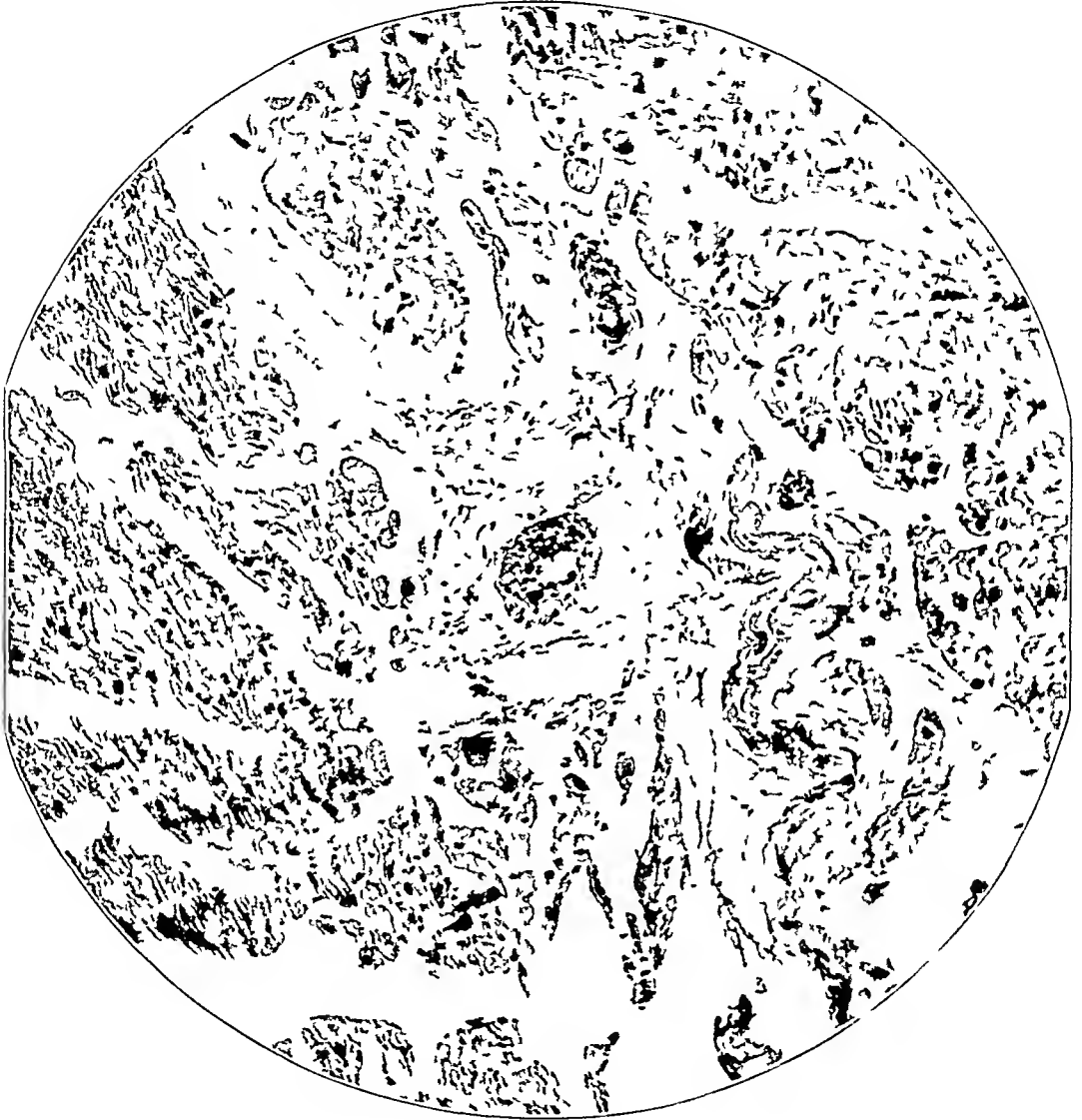


Fig. 3—Intrinsic arteries with marked sclerosis. In case 3 the lesion was diffuse, in case 5, focal.

In the latter part of February and early March she had several attacks of precordial pain, dyspnea and vomiting. These attacks were usually accompanied by a rise in temperature from 100 to 101.8 F. Once the temperature fell to 96.4 F. These episodes lasted for two to three days. About the middle of March she had a severe pain in the right leg which persisted for three days. A few days later she had a severe pain in the left side of the chest followed by a slight cough.

The first heart sound was muffled, followed by a soft blowing systolic murmur. At the aortic area there was a soft blowing to-and-fro murmur. The pulmonic second sound was much accentuated. A pericardial friction rub was present to the left of the sternum. The liver became enlarged and tender again, and the ankles edematous. Râles developed at the bases of the lungs. Venous congestion of the neck was absent. Twenty-four cubic centimeters of tincture of digitalis was given between February 1 and March 26, inclusive. Until April the precordial pain recurred frequently, but varied greatly in intensity. The temperature varied from 98.6 to 102.6 F. By April 5 the clinical improvement was marked, the physical signs remained practically unchanged. Later in the month, a rise in temperature occurred which lasted for three days, the calves were tender to slight pressure but revealed no abnormalities. The patient was given 74 cc of tincture of digitalis between April 10 and May 8. Attacks of paroxysmal auricular fibrillation developed with a ventricular rate of 80. Following the appearance of fibrillation, the administration of digitalis was discontinued, and the heart returned to its normal sinus rhythm, with a rate of 107. These attacks of paroxysmal auricular fibrillation recurred for a period of hours to a few days. Dyspnea was extreme, but was not accompanied by cyanosis. The systolic blood pressure remained at 120 mm of mercury, the diastolic pressure was difficult to obtain. The temperature rose to 102 and 103 F, returning to normal between the attacks of pain and dyspnea. The liver increased rapidly in size and pulsated. At one time pain was elicited over the spleen. Following one attack of severe pain in the left shoulder and axilla, a massive swelling of the arm rapidly appeared, extending up into the neck and later into the right arm. A cordlike mass was palpable on the left side extending up into the neck. General edema developed with cyanosis. The harsh character of the cardiac murmurs appeared from time to time. Death occurred in congestive failure on July 22.

Roentgen examination showed marked enlargement of the left auricle (appearing as a double shadow on the right border of the heart), left ventricular enlargement and right ventricular enlargement. The right auricle was moderately enlarged. The main branches of the pulmonary vessels were widened. The base of the aorta was not widened, although later it was definitely widened, showing the shadow of the superior vena cava to the right of the aorta.

Electrocardiographic study showed normal sinus rhythm, with one tracing of paroxysmal auricular fibrillation following poisoning with digitalis, normal sinus rhythm in a later tracing after digitalis was discontinued, diphasic T waves in leads 1 and 2 with a constantly inverted T wave in lead 3, and slurring of the ventricular complexes.

The clinical diagnosis was chronic rheumatic endocarditis, mitral stenosis, and thrombosis of the subclavian veins. The anatomic diagnosis was chronic rheumatic endocarditis, thromboses of the superior vena cava and tributaries, mural thromboses of the tributaries of the superior mesenteric vein and of the portal vein, thrombosis of the splenic vein, old and recent pulmonary thromboses, general passive congestion, and syphilis of the aorta.

This case was one of rheumatic infection with a severe course and widely scattered venous thromboses. The syphilitic element was asymptomatic.

CASE 3—F. B., a Negro, 34 years old, was admitted to the City Hospital on May 16, 1928, because of dyspnea, pains in the joints and edema of the legs. At the age of 23, he had a chancre, one year later, an attack of acute polyarthritis, and one year later, acute gonorrhea.

On physical examination he appeared acutely ill, and was moderately dyspneic. The pupils were normal, the pharynx was injected and the cervical glands palpable. Percussion revealed enlargement of the heart. A short presystolic, a systolic and a diastolic murmur were present at the apex. The pulmonic second sound was louder than the aortic second sound. The blood pressure was 120 systolic and from 50 to 0 diastolic. The liver was tender and was enlarged two fingerbreadths.

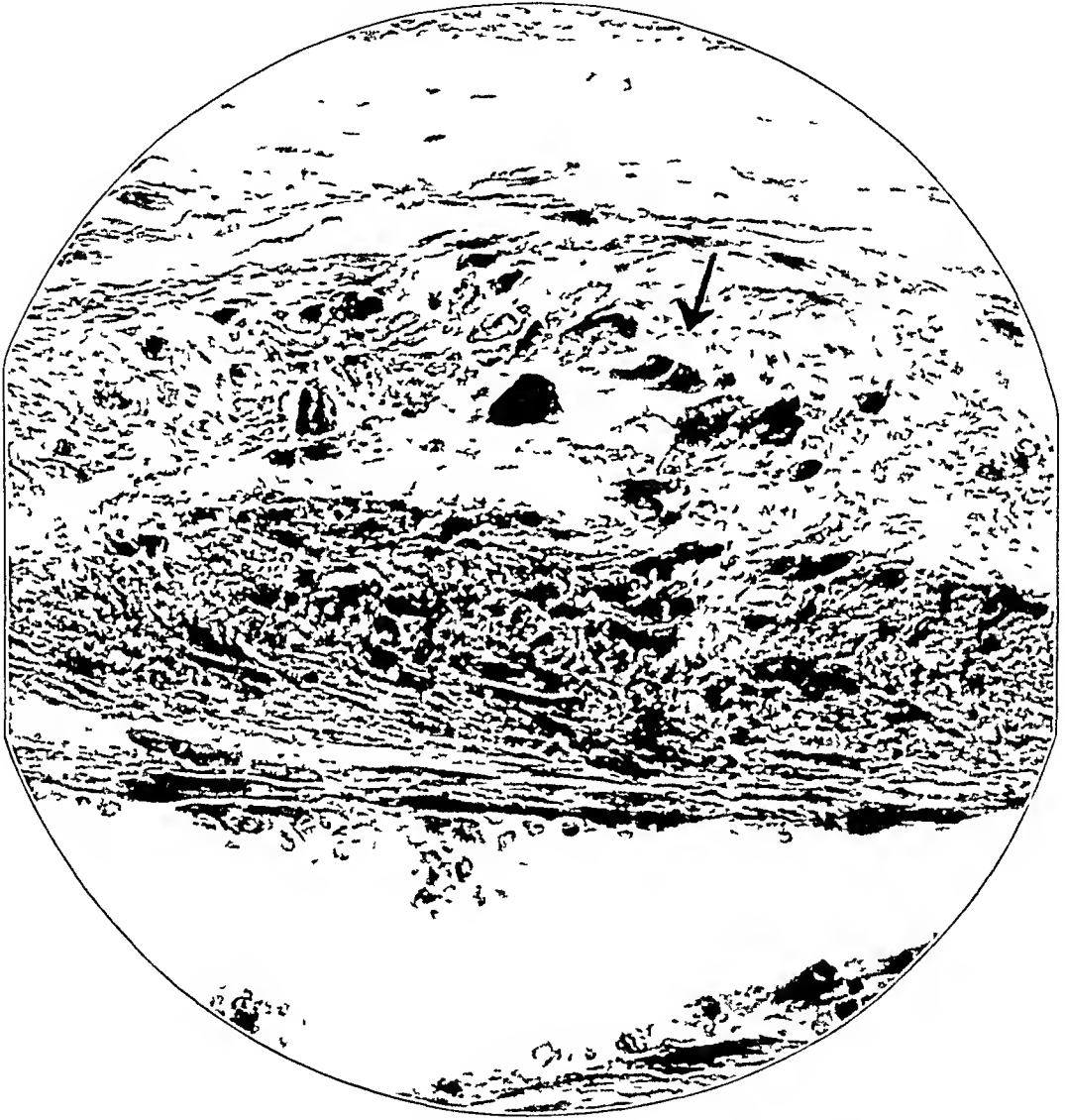


Fig 4—In the perivascular connective tissue is a group of Aschoff cells, indicated by the arrow.

below the costal margin. The spleen was palpable and tender. The Wassermann reaction was 4 plus. The urine was normal. The temperature varied from 97 to 100 F. The patient was discharged on July 9, much improved.

The second period of hospitalization was from August 6 to Feb 14 1929. For two weeks after leaving the hospital he remained well. Then there occurred a sudden onset of substernal pain and shortness of breath. The pupils were normal.

The fundi revealed sclerotic vessels. At the apex was a loud systolic, a long diastolic and a suggestive presystolic murmur. The pulmonic second sound was much accentuated and louder than the aortic second sound. There was a long diastolic murmur at the aortic area. The aortic second sound was present, but faint. The blood pressure was 110 systolic and 80 diastolic. The Wassermann reaction was 4 plus. The urine was normal. The temperature was normal. The

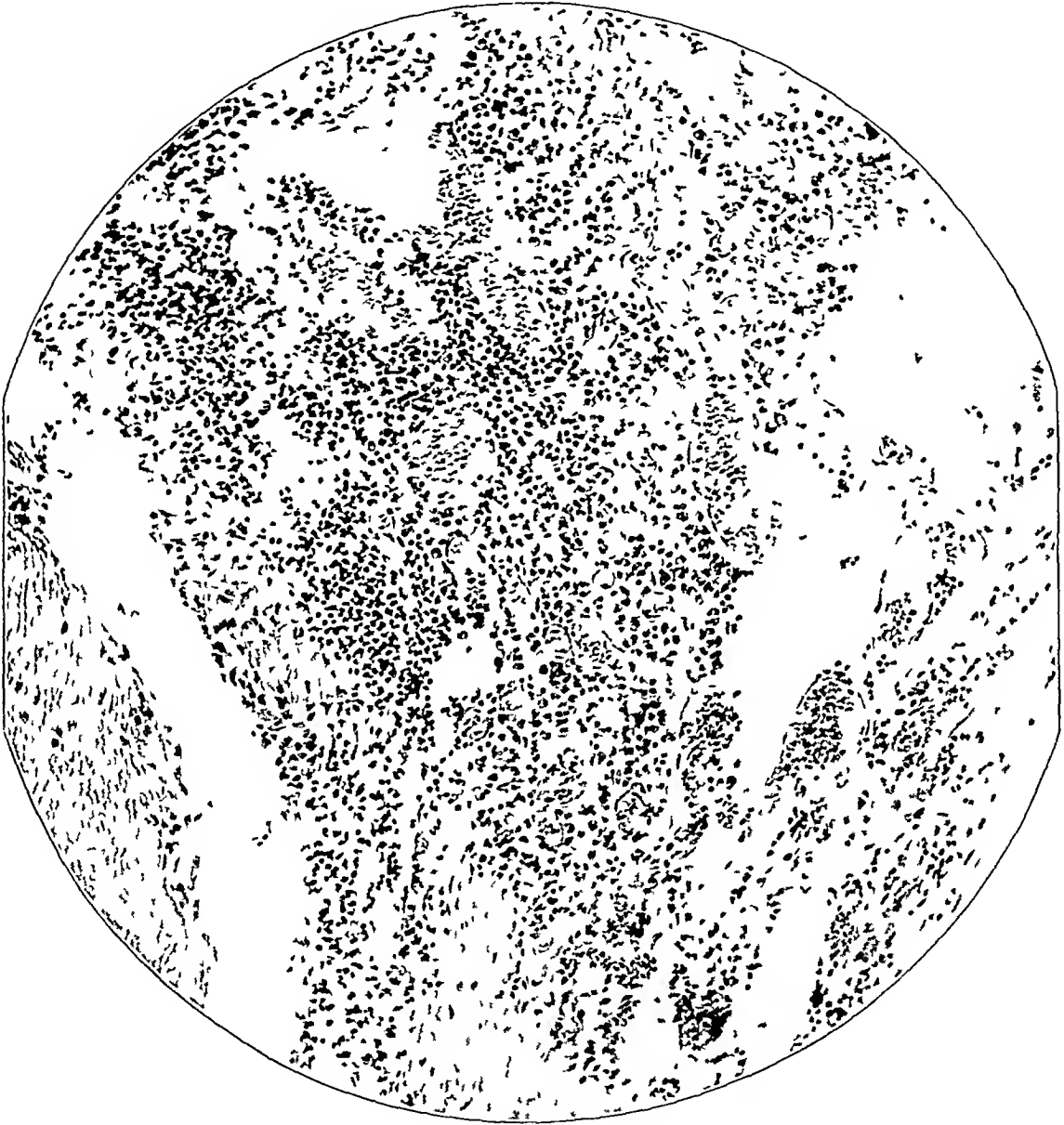


Fig 5 (case 6) —The inflammatory lesion of the aorta at the base

patient was fairly comfortable and compensation was good until the latter part of November. From that time until he left the hospital he had many attacks of paroxysmal dyspnea accompanied by a sensation of choking, usually with pain and usually nocturnal, sometimes diurnal. At first the attacks were not frequent, but at times several would occur in a twenty-four hour period. A distinct diastolic and a loud blowing systolic murmur were heard at the aortic area on some occasions. Once he had acute pharyngitis and adenitis, and a pericardial friction was detected

From November onward the temperature varied from 98 to 100 F. The pulse rate varied from 110 to 120, being higher proportionately than the temperature. On discharge he was quite comfortable.

The third admission was on May 7, 1929. In April, the attacks of palpitation and dyspnea recurred, and he became very short of breath. He was distinctly orthopneic. Percussion revealed the heart larger than on the previous admissions. A thrill was present over the entire precordium. There were a loud systolic and a presystolic murmur at the apex. The aortic region was normal. The pulmonic second sound was greater than the aortic second sound. The blood pressure was 98 systolic and 62 diastolic. The Wassermann reaction was 4 plus. The urine had a specific gravity of 1.014 and a few casts. The liver was large and tender. The temperature until death, on May 16, was slightly irregular. The outstanding symptom was frequent attacks of paroxysmal dyspnea, some attacks accompanied by precordial pain. Death occurred suddenly.

The roentgen examination revealed enlargement of all the chambers of the heart. The base of the aorta on May 18, 1928, was not widened. Widening of the aorta was seen on August 18. The pulmonary fields showed evidence of chronic pulmonary stasis with secondary fibrosis. The main branches of the pulmonary vessels were widened.

Electrocardiographic study showed normal sinus rhythm, auriculoventricular conduction time top normal (0.2 seconds), a diphasic T wave in lead 2 in one tracing, and no definite evidence of coronary disease in the T wave deflections. The ventricular complexes showed slight slurring. No axis deviation to right or left was present, but a large S wave was present in both tracings taken.

The clinical diagnosis was rheumatic pancarditis, mitral stenosis and insufficiency, pulmonary tuberculosis and syphilis. The anatomic diagnosis was chronic rheumatic endocarditis, diffuse sclerosis of the intrinsic coronary arteries, and syphilis of the aorta.

This case was one of latent rheumatic infection which became evident after a syphilitic infection, progressing slowly, with the development of disease of the small vessels of the coronary system, which dominated the clinical course during the last few months.

CASE 4—J. M., a man 37 years old, was admitted to the City Hospital on Jan. 3, 1928, because of abdominal swelling and shortness of breath. A history of syphilis and rheumatic fever was denied. He was well until one year previously when he had lobar pneumonia. Since then he had had a chronic cough, at times with a blood-streaked sputum, and later gradually increasing dyspnea and swelling of the abdomen. He was hospitalized in December 1927. Examination at that time showed marked orthopnea and dyspnea, arcus senilis and pupils fixed to light and in accommodation. There was dullness at the bases of both lungs, with enlargement of the heart, the apex being in the sixth interspace in the anterior axillary line. The heart sounds were diminished in intensity. The blood pressure was 130 systolic and 90 diastolic. The Wassermann reaction was negative. There were 18,000 white blood cells with 77 per cent polymorphonuclears. On fluoroscopy the aortic area was seen to be widened.

For three weeks before admission he had gradually increasing dyspnea. He was moderately comfortable. There were signs of moderate decompensation and ascites. The blood pressure was 105 systolic and 75 diastolic. The Wassermann reaction was 4 plus. The heart sounds were weak, and the heart rate 120. The second sound was replaced by a loud murmur filling the entire diastole. The liver

was enlarged to the umbilicus and was tender, a fluid wave was present. The fingers were clubbed. The eyegrounds showed marked sclerosis. The urine, at first normal, later showed large amounts of albumin, casts and white blood cells. The patient remained moderately comfortable until January 25, when his temperature rose to 103 F with signs of lobar pneumonia. He died three days later, on January 27.

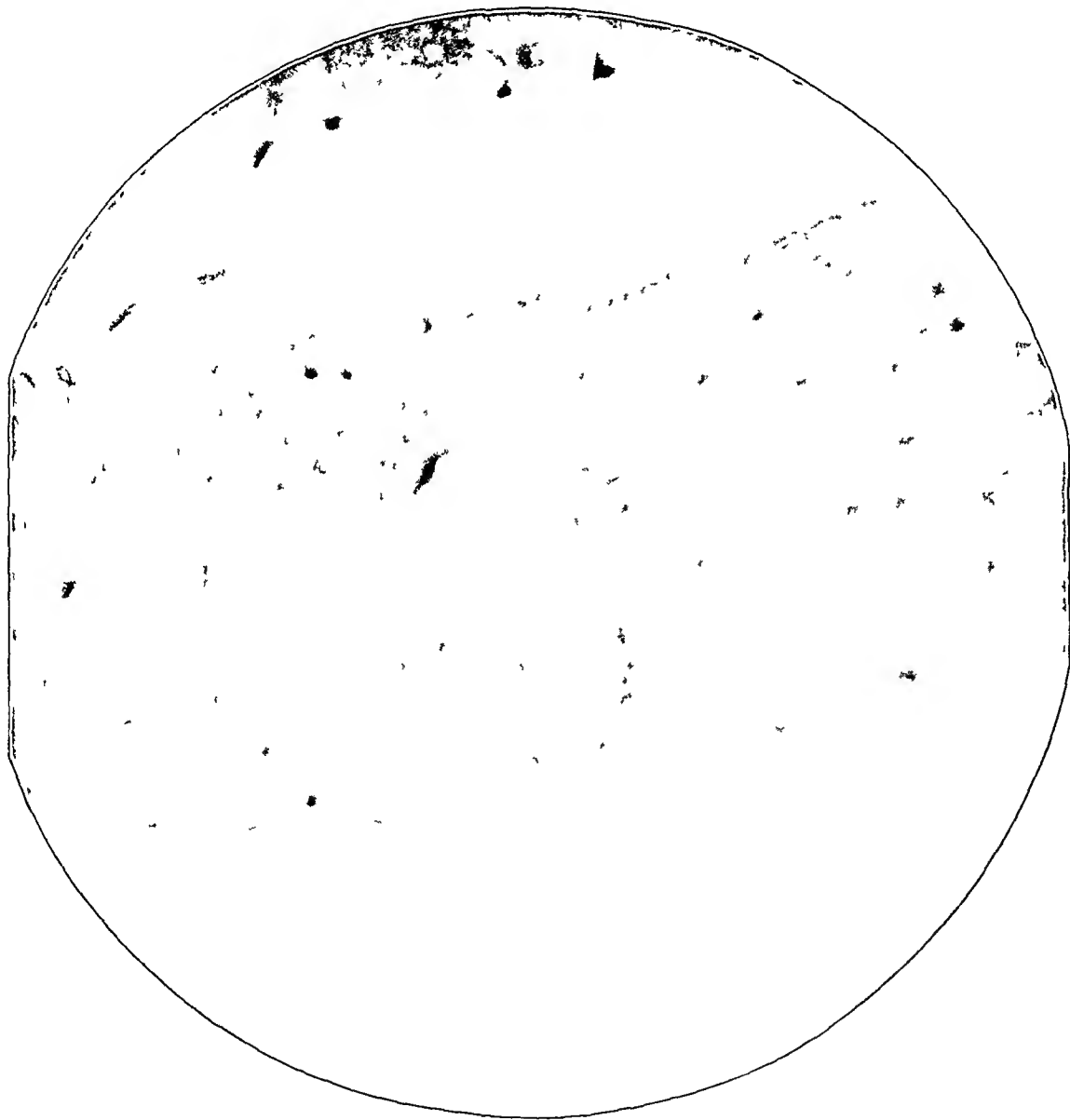


Fig 6 (case 6) —Left branch of the conduction system, showing the marked edema of the fibers. At the edge of the section is a small portion of the cardiac muscle.

Röntgen examination showed moderate enlargement of the chambers of the heart, with slight sclerosis of the aorta, engorgement of the pulmonary vessels and evidences of chronic pulmonary infection.

Electrocardiographic study showed normal sinus rhythm, tachycardia, a low voltage T wave and slurring of the ventricular complexes. The clinical diagnosis

was rheumatic heart disease, chronic endocarditis, mitral stenosis and insufficiency, syphilitic aortitis, and acute lobar pneumonia. The anatomic diagnosis was chronic rheumatic pancarditis, syphilis of the aorta, chronic passive congestion, healed tuberculosis, and acute lobar pneumonia.

This was a case of a mildly decompensated rheumatic heart with syphilis of the aorta, in which an intercurrent infection developed which caused death.

CASE 5—L. G., a white man, aged 44, was admitted to the City Hospital on April 25, 1929. At the age of 33 he contracted syphilis. At 34 he had an attack

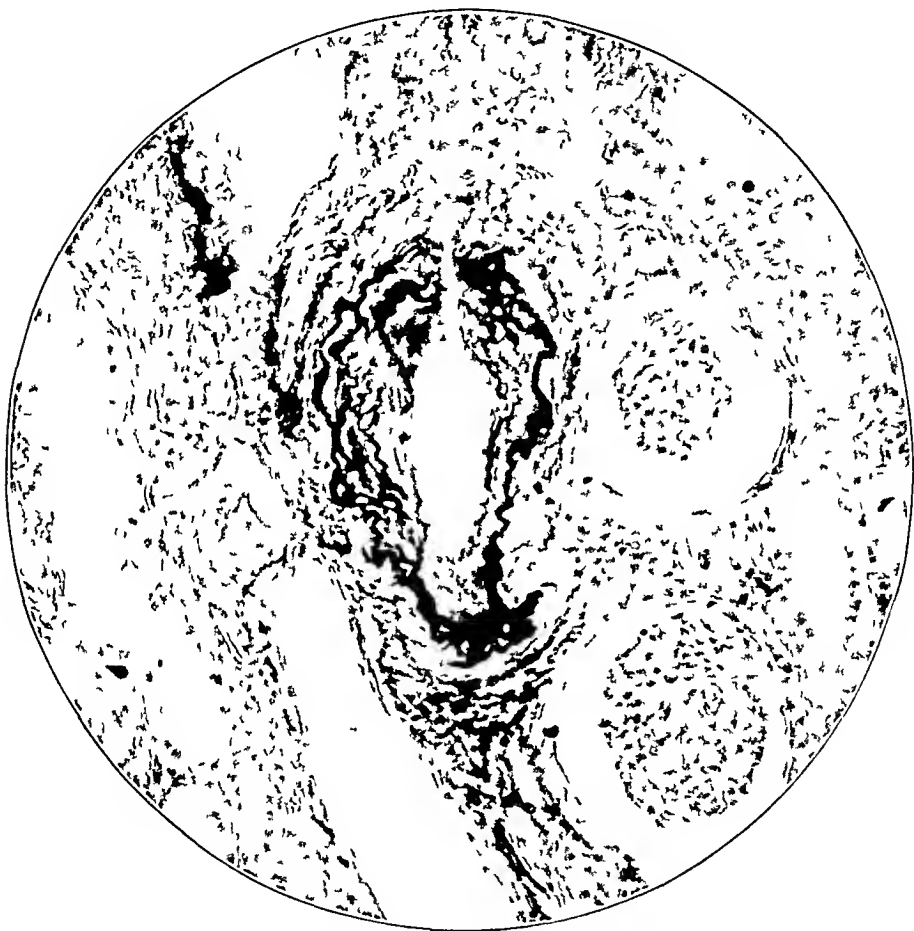


Fig. 7 (case 5)—Arterial lesion in the kidney. The photomicrograph shows the splitting of the internal elastica of an interlobular artery.

of polyarthritis. He remained well until December 1928, about nine years later. He entered the hospital because of dyspnea and precordial pain on exertion. The Wassermann reaction was 4 plus. He remained in the hospital about two weeks and then resumed his work as a laborer. For almost three months he remained well, but late in March, pains in the left side of the chest recurred, with swelling of the abdomen and legs.

On readmission to the City Hospital the physical signs were ascites, edema of the legs, venous pulsations of the vessels of the neck, dulness at the base of the right lung and râles. There was a blowing systolic murmur at the apex and a totally irregular pulse. The liver was four fingerbreadths below the costal

margin The Wassermann reaction was 4 plus There was again congestive failure A loud blowing systolic murmur was heard over the entire precordium The apex beat was diffuse in the sixth interspace in the anterior axillary line There was no thrill or diastolic murmur The aortic second sound was moderately accentuated, roughened and snapping The pulse rate was 60 and totally irregular, and the blood pressure was 115 systolic and 75 diastolic The liver was one fingerbreadth below the costal margin The fingers were clubbed and cyanosed The Wassermann reaction was 4 plus The pupils were normal For a few days, the temperature was irregular, ranging from 100 to 101 F, and then dropped to 97.8 F

Late in May he had a few attacks of paroxysmal dyspnea He was given 34 cc of tincture of digitalis between May 31 and June 11 Complete heart block developed By June 20, after the discontinuance of digitalis, the heart returned to its usual rhythm of auricular fibrillation The blood pressure had risen to 135 systolic and 65 diastolic There was a double murmur at the apex The patient remained fairly comfortable until February, but climbing stairs always caused moderate dyspnea The blood pressure gradually rose to 146 systolic and 65 diastolic During February he had several attacks of precordial pain and dyspnea Frequently the pain was cramplike Occasionally, similar pain was present in the legs and abdomen The liver was enlarged, and became tender At times dyspnea was severe, and he would sit on the side of the bed for relief Many of the attacks were nocturnal The heart rate remained slow but pulse deficit appeared During March, cyanosis became marked, and the attacks of dyspnea were extremely frequent both day and night The blood pressure dropped to 130 systolic and 90 diastolic Congestive failure increased, and he died on March 5

The roentgen examination showed marked left ventricular enlargement, enlargement of the right ventricle, definite widening of the main branches of the pulmonary vessels and enlargement of the right and left auricles The base of the aorta was not widened

The electrocardiographic study demonstrated the change from auricular fibrillation to complete heart block with auricular fibrillation and return to chronic auricular fibrillation, with a slow ventricular rate of 60 The T wave was diphasic in leads 1 and 2, and the T wave in lead 3 became permanently inverted The QRS complex was slurred

The clinical diagnosis was rheumatic heart disease with mitral stenosis and insufficiency, and syphilitic heart disease The anatomic diagnosis was healed rheumatic endocarditis, active rheumatic myocarditis, syphilitic aortitis, general passive congestion, acute pulmonary infarction, and nephrosclerosis

This case was one of healed rheumatic lesion of the mitral valve, active rheumatic myocarditis and active syphilitic aortitis not involving the valve It was an instance of rheumatic carditis with constitutional syphilis

CASF 6—C B, a Negro, 26 years old, was admitted to the City Hospital on Aug 26, 1930, complaining of abdominal distention and pain He had always been subject to sore throat, a history of syphilis and rheumatic fever was denied For two years he had episodes of cough, palpitation, weakness and precordial pain, increasing in frequency and severity, followed by dyspnea and swelling of the abdomen

Physical examination revealed the patient to be dyspneic and acutely ill The pupils were normal The entire precordium had a wavy impulse There were double murmurs at the mitral and aortic areas A diastolic apical thrill was present The blood pressure was 130 systolic and 45 diastolic The liver was three finger-

breadths below the costal margin. The urine had a specific gravity of 1.020 and showed no albumin or casts. He had many attacks of severe pain in the chest, sometimes accompanied by bloody expectoration. The pain was sometimes pre-

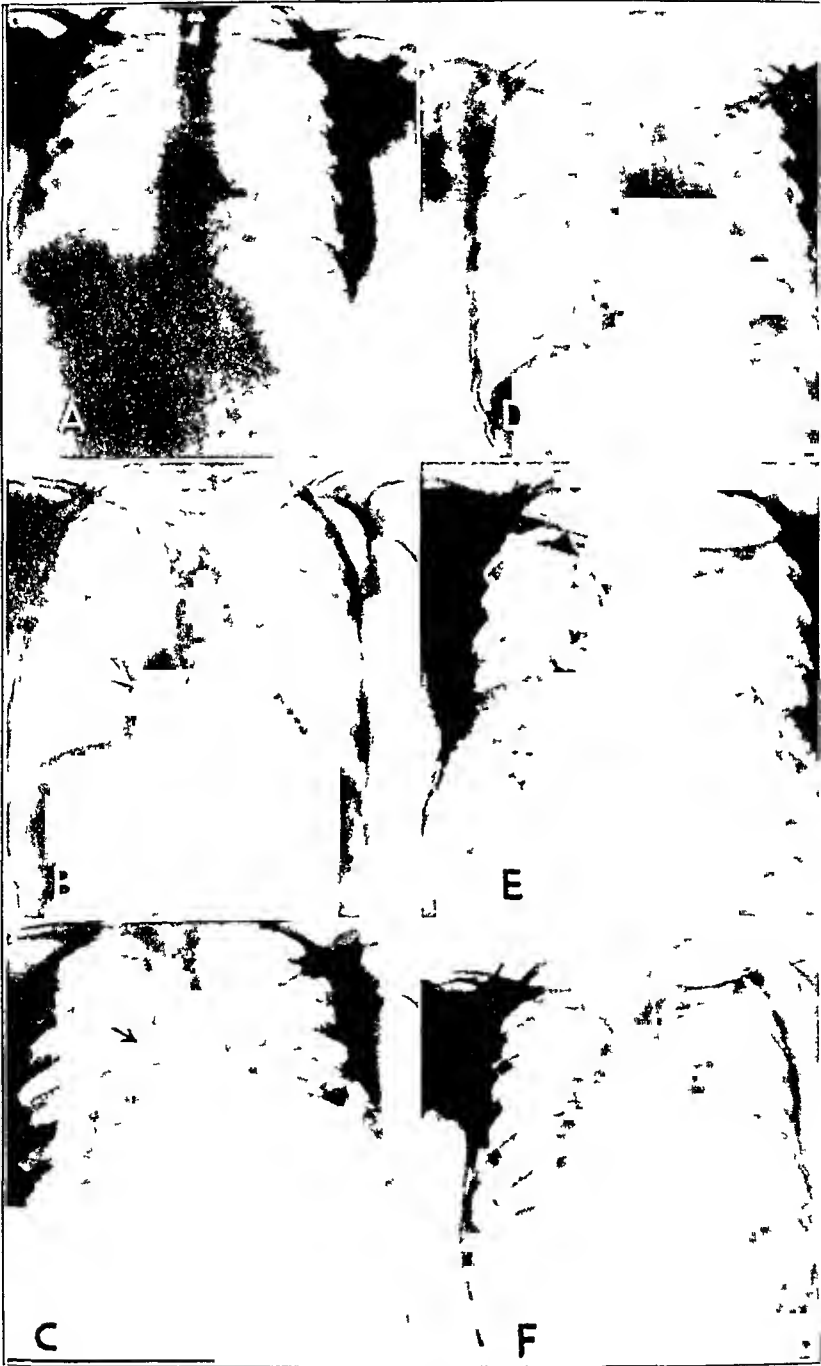


Fig 8—*A* (case 1), mitral and aortic insufficiency, *B* (case 2), appearance of the left auricle as a double shadow on the right side, *C* (case 2), shadow of the vena cava to the right of the aorta, *D* (case 3), marked pulmonary fibrosis, *E* (case 5), normal aortic and tricuspid valves, with accentuation of the ascending aortic curve, *F* (case 6), widening of the base of the aorta

cordial only, and occasionally was elicited by pressure over the precordium, usually the pain was spontaneous. Urinary observations varied from no albumin to a heavy trace and from no casts to many, with abundant red cells. The patient's mental attitude was one of apprehension, and he was frequently extremely depressed. On October 1, he had an attack of severe precordial pain, became very weak and had a bloody expectoration. He apparently improved for a short time, and then died suddenly the same day. The temperature consistently ranged from 98 to 100 F. The pulse rate was always rapid, and consistently remained above the temperature level.

Roentgen examination revealed great enlargement of the left ventricle, with some widening of the base of the aorta. The other chambers of the heart were

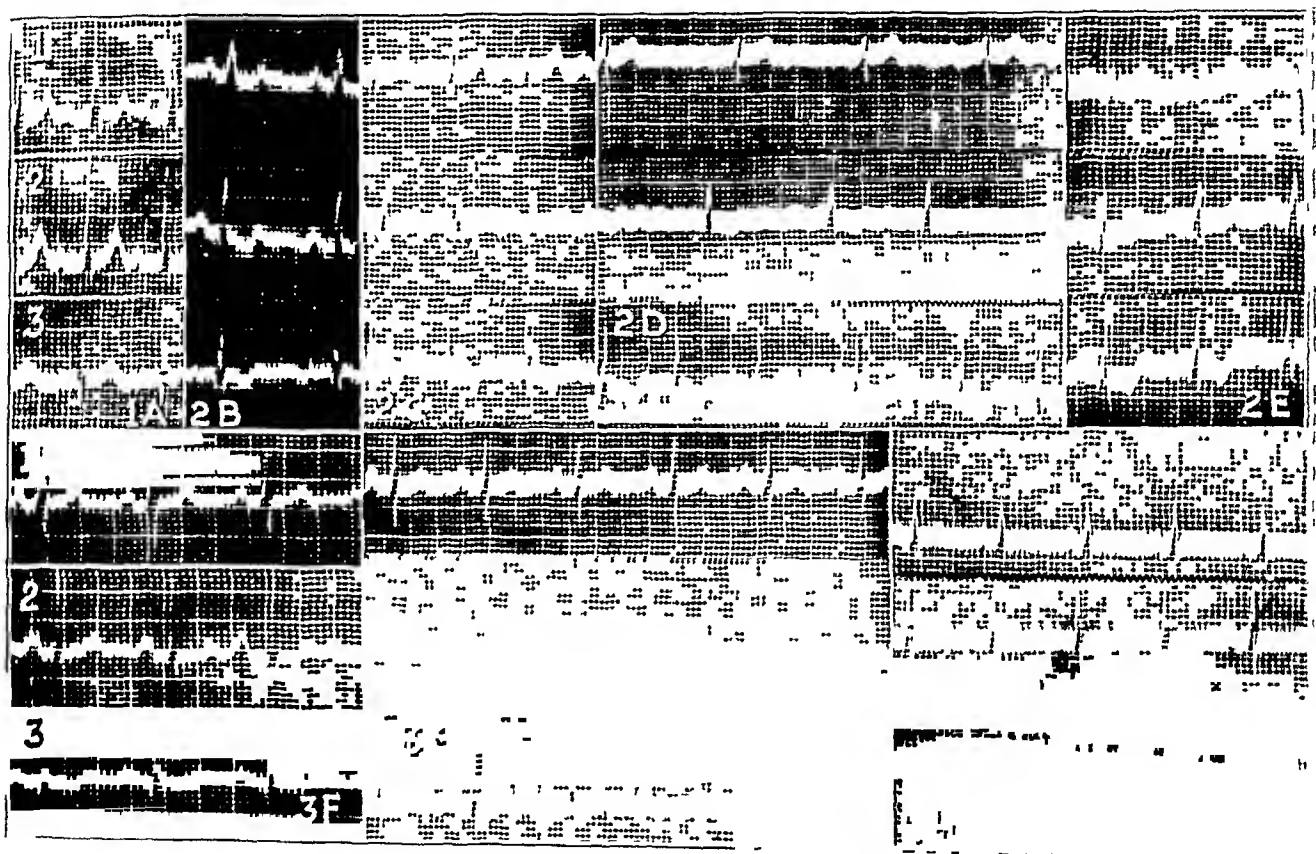


Fig 9—Electrocardiogram, showing 1A, neither left nor right axis deviation, mitral insufficiency, aortic stenosis and insufficiency, in an inspiratory type of heart, 2B, C, D, E, auricular fibrillation following treatment with digitalis, with a constantly inverted T wave in lead 3, 3F, slight Q wave in lead 3 and a diphasic T wave in lead 3, 3G, no Q wave in lead 3, but an upright T wave, 4H, a low voltage T wave

enlarged. The definite widening of the base of the aorta and the type of heart showing aortic insufficiency, with the clinical findings, seemed evidence of the involvement of syphilis of the aortic valve.

The electrocardiographic study showed normal sinus rhythm, with a top normal auriculoventricular conduction time (0.2 second), slurring and notching of the QRS complexes, and the development of an inverted T wave in leads 2 and 3.

The clinical diagnosis was syphilitic aortitis, with aortic insufficiency, rheumatic heart disease, mitral stenosis and insufficiency, and coronary disease. The anatomic diagnosis was chronic rheumatic endocarditis, chronic mural endocarditis, acute interstitial myocarditis, syphilitic aortitis involving the aortic valve, recent pulmonary infarctions, acute lobar pneumonia, and acute fibrinous peritonitis.

This case was one of rheumatic heart disease in which the rheumatic lesions were predominantly inflammatory, and the syphilitic involvement of the aortic valve profound. Superimposed was an acute generalized infection.

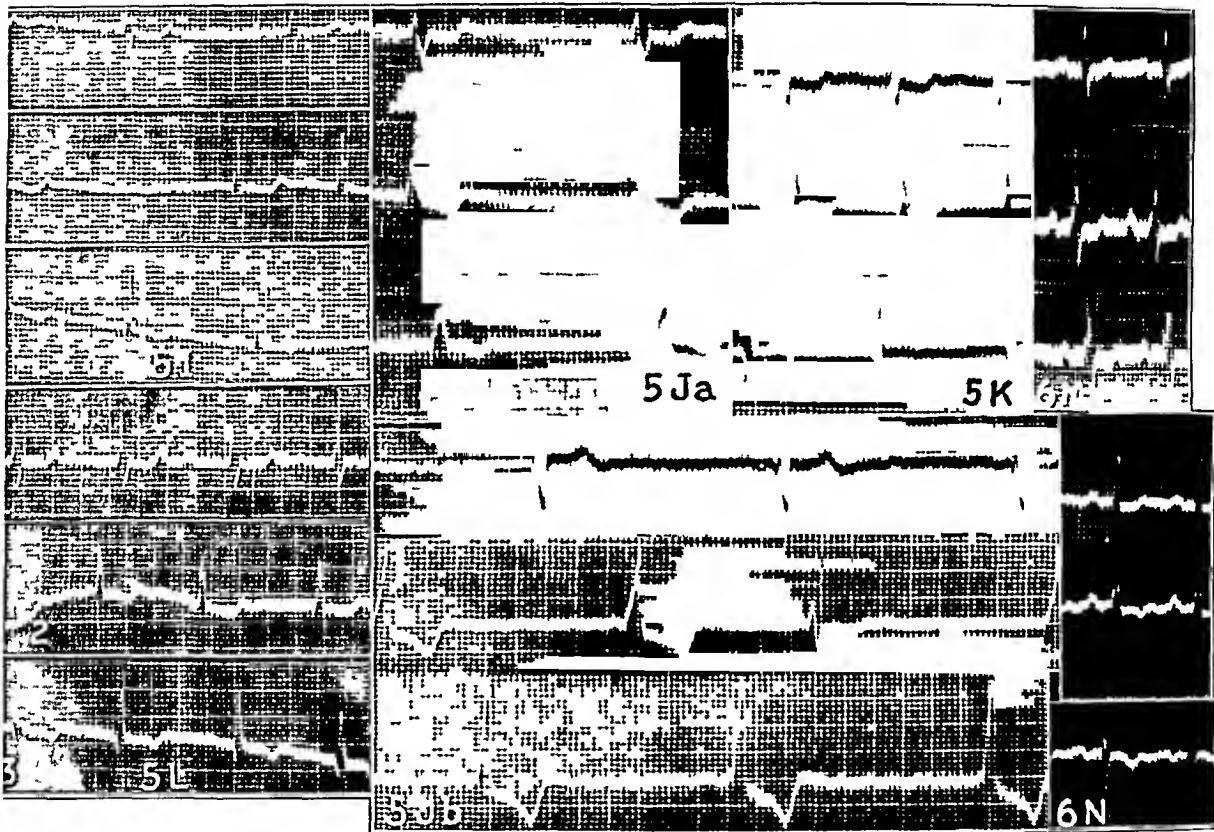


Fig 10—Electrocardiograms, showing 5I auricular fibrillation, 5Ja, usual leads, 5K, direct chest leads with complete auriculoventricular dissociation, bundle branch block following digitalis and one returning cycle of usual rhythm, 5L, return to the usual rhythm with the Q wave not present in 5I, 6M, diphasic T wave in leads 2 and 3, 6N, inverted T wave in leads 2 and 3 and marked notching in lead 2 of the QRS complex.

PATHOLOGIC ANATOMY

The criteria used for the diagnosis of rheumatic heart disease were valvular involvement by a productive and inflammatory lesion tending to affect the mitral, aortic, tricuspid and pulmonic valves, and in that sequence, active pericarditis, and the presence of Aschoff bodies. For the diagnosis of syphilis the criteria used were widening of the com-

missures, endarteritis of the vasa vasorum, narrowing of the mouths of the coronary arteries, and a pigskin-like appearance of the intima of the aorta. Great stress was placed on the gross and microscopic appearance of the commissures. The separation of the attachments of the cusps, the thickening of the leaflets, the pearly appearance of the intima and the endarteritis of the vasa vasorum with perivascular infiltration by lymphatic and plasma cells were considered characteristic of syphilis. These lesions have also been stressed by Saphir and Scott⁶ and by Martland.⁷ In control series of (1) rheumatic hearts and (2) hearts of syphilitic patients this commissural lesion was not found in the first group and almost invariably in the second. Spirochetes were not found in any case by the Jahnke and Warthin-Starry methods. The pathologic processes are summarized in table 1.

Hypertrophy was a feature common to all cases of the present group. The greatest weight occurred in the youngest patient (case 1), who had pancarditis. In the other extremely large heart (case 5), the absence of either active adhesive pericarditis or a valvular aortic lesion suggested the possibility of preexisting hypertension, histologic study of the kidney revealed benign nephrosclerosis.

The lesions due to rheumatic infection were marked in all six cases. There was adhesive pericarditis in two cases. Valvulitis was present in all. The mitral valve was involved in the entire series, the aorta in four cases, the tricuspid valve in four and the pulmonic valve in three. Myocardial Aschoff bodies were present in all but one case. Definite lesions of syphilis were limited to the aortic commissures in five instances, it was the predominant lesion in only one case. In two cases there was an intensely acute interstitial myocarditis, suggesting a terminal infection.

Stenosis of the mouths of the coronary arteries, so common in syphilis, was present in only half of the cases, these cases also showed the most marked widening of the commissures. Marked atherosclerosis of the main coronary arteries was present in three cases, in one instance with an active perivascular reaction. The patient in this case had clinical and classic attacks of paroxysmal dyspnea. Focal sclerosis was found in the patient with the renal changes of benign nephrosclerosis. This patient also had attacks of paroxysmal dyspnea and cardiac pain.

CLINICAL FEATURES

Race, Sex and Age—Five of the patients were colored, three were men and two women. The only white patient was a man. The ages

⁶ Saphir, C., and Scott, R. W. Involvement of the Aortic Valve in Syphilitic Aortitis, *Am J Path* **3** 527, 1927.

⁷ Martland, H. S. Syphilis of Aorta and Heart, *Am Heart J* **6** 1, 1930.

TABLE 1—*Pathologic Processes in Hearts of Six Patients with Syphilitic and Rheumatic Infection*

Case	Weight, Gm	Pericardium	Valves				Commis- sure	Myocardium	Endocardium	Coronary Arteries		Intrinsic Sclerosis
			Mitral	Aortic	Tricuspid	Pulmonic				Mouth	Main	
1	1,050	Adherent, rheumatic	Active rheu- matic lesion, incompetent	Active mixed lesion, calcified, stenosis	Active rheu- matic, stenosis	Rheumatic (microscopic) Aschoff bodies	Grossly normal, endarteritis of vasa vasorum	Gross apical scar, per- vascular scar, acute interstitial myocarditis	Mural throm- boses of left auricle, microscopic evidence of mixed cells	Normal	Moderate atheroma	In old scars
2	500	Nonspecific, visceral	Active rheu- matic lesion, calcified, stenotic	Active rheu- matic lesion, calcified, stenosis	Active rheu- matic lesion, stenosis	Young vege- tations	Slight widen- ing, endarteritis	Perivascular scar, mil- itary scar, Aschoff bodies	Mural throm- boses of left auricle	Normal	Moderate atheroma	Normal
3	600	Normal	Healed stenotic	Active rheu- matic lesion, stenosis	Active rheu- matic lesion, stenosis	Normal	Marked widen- ing, endarteritis	Same as 2	Mixed cell foel (micro- scopic)	Stenosis	Moderate atheroma	Diffuse sclerosis
4	600	Adherent, rheumatic	Active rheu- matic lesion, stenotic	Young lesion, competent	Normal	Rheumatic (microscopic)	Moderate widen- ing, endarteritis	Same as 2	Same as 3	Stenosis	Athero- fibrosis, marked perivascular inflammation	Sclerosis in scars
5	800	Nonspecific, visceral	Healed stenotic	Normal	Normal	Normal	Normal, syphilitic nortitis above valve	Perivascular scar, focal and diffuse Aschoff bodies	Dense foel of lympho- cytes	Normal	Intense sclerosis	Focal sclerosis
6	500	Nonspecific, visceral	Active rheu- matic lesion, incompetent	Syphilitic and rheumatic incompetent	Early vege- tations	Normal	Marked widen- ing, endarteritis	Perivascular scar, Aschoff bodies, acute interstitial myocarditis	Small fibrotic nodules	Marked stenosis	Marked atheroma	Normal

varied from the second to the fifth decades, 16, 26, 25, 34, 27 and 44 years

Order of Appearance of Infections—Rheumatic fever definitely preceded the syphilis in one case, and probably preceded it in another. The chancre appeared one year previous to the first attack of rheumatic fever in two instances. A history of rheumatic fever or of syphilis could not be elicited in two cases. The onset of a first attack of rheumatic fever relatively late in life following syphilitic infection was an interesting feature. Two hypotheses may be advanced to explain this phenomenon. 1. The syphilitic lesion rendered easier the secondary invasion by the rheumatic agent. Warthin⁸ believed that latent syphilis in a young person predisposes him to secondary bacterial endocarditis. Coombs⁹ likewise was of the opinion that the syphilitic valve is disposed to secondary invasion. Secondary invasion of the syphilitic valve resulting in the productive and inflammatory changes characteristic of rheumatic infection is, in our experience, uncommon. As suggested by Griggs,¹⁰ the syphilitic process, by the very nature of endarteritis, automatically closes by the normal course of its evolution the portals of entry to secondary invaders. 2. The syphilitic process may cause an exacerbation of sufficient intensity of a low grade asymptomatic rheumatic disease to result in its passage over the threshold of clinical manifestation. The view generally held that the primary infection of rheumatic disease is acquired in the early years of life lends support to the second hypothesis.

In the four cases with sufficient data, the interval of time between the second infection, as based on the appearance of clinical symptoms, whether of syphilis or rheumatic fever, and the onset of the first appearance of cardiac decompensation was usually short, from three months to two years. In one case, mild decompensation occurred shortly before the syphilitic infection, to be followed in six months by a severe break. This is in contrast to the usual clinical course of uncomplicated rheumatic heart disease, and parallels the two cases mentioned. Only once was there a long interval, nine years. The patient acquired syphilis at the age of 33, a much later age than the others, rheumatic fever occurred at 34. The cardiac break, although delayed, occurred at a shorter interval than is usual in uncomplicated syphilis.

Course—The clinical course of the disease was rapidly progressive after the first break in compensation, regardless of therapy. With one

⁸ Warthin, A. S. Lesions of Latent Syphilis, *Brit. M. J.* 2:236 (Aug. 10) 1929.

⁹ Coombs, C. F. Syphilis of Heart and Great Vessels, *Lancet* 2:236, 1930.

¹⁰ Griggs, LeRoy H. Bacterial Endocarditis as a Sequel to Syphilitic Valve Defect, *Am. J. M. Sc.* 164:275, 1922.

exception it terminated within two years, and usually within one. One patient lived for ten months, two for one year, one for one and a half years and one for two years. In only one instance was there a long duration, seven years. The patient had frequent, easily precipitated cardiac breaks, and never attained well established compensation. The serious clinical course corresponds closely to the observations of Fordyce. In his series, the patients were reacting poorly to the rheumatic disease, and improved only when antisyphilitic therapy was instituted. In the present series, antisyphilitic therapy was much less efficacious, whether used intensively or conservatively. The explanation of the difference in the results possibly depends on the manifestations of syphilis in the congenital form, aortic involvement is rare, in the acquired form, very common. Two factors, both tending to attack the cardiovascular system, are active in the present series. As pointed out by Pearse,¹¹ in experimental vaccinia and syphilis in the rabbit, the presence of concomitant active infections in the same animal may intensify the manifestations of each. The expectancy of life in our series of combined syphilis and rheumatic infection of the heart and great vessels resembled that of syphilitic persons of older years, with aortic insufficiency and congestive failure.

The direct cause of death was usually congestive failure. Two patients died suddenly, one, with a regurgitant lesion, had an extremely active inflammatory lesion and terminal suppurative myocarditis of undetermined etiology and the other died of diffuse sclerosis of the intrinsic coronary arteries. Intercurrent pneumonia terminated another case of mild decompensation. Table 2 gives in brief the essential features of the time element.

Pain—Pain is one of the earliest symptoms of cardiac dysfunction, and may be difficult to interpret. It may vary from simple fatigue bordering on the threshold of pain to the anginal syndrome with the classic radiation. Certain rather definite clinical pictures are present with the various types of pain. In the anginal syndrome the pain may vary from a sense of constriction only, as described by White,¹² to the agonizing pain with the segmental distribution of Head¹³ and Mackenzie.¹⁴ For purposes of description this may be called the small vessel type of pain, and may be dependent on disease of the coronary

11 Pearse, L. Reciprocal Effects of Concomitant Infections, *J. Exper. Med.* **47** 611, 1928.

12 White, P. D. Medical Treatment of Angina Pectoris, *Ann. Int. Med.* **7** 218 (Aug.) 1933.

13 Head, H. *Studies in Neurology*, New York, Oxford University Press, 1920.

14 Mackenzie, J. *Angina Pectoris*, New York, Oxford University Press, 1923.

arteries, particularly of the smaller radicles of the coronary circulation, the intrinsic myocardial vessels. Another type of anginal pain is limited to the precordium, and has possibly the same basic pathologic process. The aortic type of pain may be described as the large vessel type of pain, and is possibly due to increased intravascular tension associated with inflammatory disease of the wall of the vessels. It is frequently substernal and localized. In syphilitic aortitis the pain tends to be boring, substernal and localized. At times it is nocturnal, when it is possibly due to circulatory changes of the cardiorespiratory phenomena during sleep, which are of chemical and mechanical origin. Intravascular changes of pressure are probably basic factors. In aneurysms,

TABLE 2—*The Time Element in Syphilitic and Rheumatic Infection*

Case	Relationship of Syphilis and Rheumatic Fever	Free Period Between Second Infection and First Cardiac Break	Age at Onset of Congestive Failure, Years	Duration of Course	Cause of Death
1	Rheumatic fever plus syphilis	Preceded syphilis, second break in 6 months	15	1½ yrs	Congestive failure
2	Rheumatic fever (?) plus syphilis	3 months	25	10 mos	Congestive failure
3	Syphilis plus rheumatic fever	2 years	27	7 yrs	Congestive failure with sudden death
4	?	?	36	1 yr	Lobar pneumonia
5	Syphilis plus rheumatic fever	9 years	43	1 yr	Congestive failure
6	?	?	24	2 yrs	Congestive failure with sudden death

there is an added factor of pressure on surrounding structures. Occasionally, aneurysm is associated with axillary pain, probably due to extension of the syphilitic process to the aortic branches. Clinical observation of a patient of McCarthy¹⁵ in arteriovenous anastomosis for the relief of aortic aneurysm demonstrated a shift of the pain from right to left, the opposite side, owing to the change of intra-aortic pressure subsequent to the operative procedure. In aortic arteriosclerosis the pain is much milder than in syphilis, but has the same distribution.

The type of pain accompanying rheumatic infection is of a different character. It is recurrent, probing and usually limited to the pre-

¹⁵ McCarthy, P. A. Treatment of Aneurysms of the Thoracic Aorta and Innominate Artery by Distal Arterio-Venous Anastomosis, *Ann Surg* 91 161, 1930

cordium, and does not tend to radiate. Frequently it is limited to the region of the apex. It is intensified by pressure over the region. During periods of exacerbation of the rheumatic infection it is more prominent. Rheumatic hearts with advanced mitral disease sometimes have the true anginal syndrome, possibly due to combined coronary disease, inflammation of the large vessels and pressure phenomena, as of a large left auricle.⁵ Sweeny's¹⁶ patient with mitral stenosis was relieved only by morphine and cervical sympathectomy. Rarely, the patient experiences pain over the pulmonary artery, this region is not tender to pressure, but the pulmonic area on fluoroscopic examination appears dilated. Possibly the clinical observation rests on the presence of an inflammatory lesion of the region, with increased intravascular tension. Arthritic pains, pain in the vessels due to thromboses, pain in the lungs and splenic pain resulting from thromboses of the organs accompany rheumatic infection in heart disease. The pain accompanying rheumatic heart disease may be compared to that elicited over any area of inflammation, and may be described as an infectious type of pain.

In the present series, pain was present in five cases. In three it was a prominent feature. In only one case was there pain in the joints. It was of the infectious type in two other cases, both with extremely active lesions, one with multiple thromboses. It was of the precordial anginal type in another case, which developed during the course of the illness and dominated the picture during the last few months. This patient also had attacks of paroxysmal dyspnea. Histologic study later revealed generalized sclerosis of the intrinsic coronary arteries. Another patient had cardiac pain with attacks of dyspnea in which the pain disappeared with progressive congestive failure.

The only patient with aortic regurgitation predominantly syphilitic had the aortic type of pain in the chest accompanied by bloody expectoration. He did not have axillary pain, which sometimes accompanies disease of the aorta and its branches, he had the coronary type of pain and also abdominal pain.

Dyspnea—Dyspnea in cardiac disease is usually of the congestive failure type, at times it is paroxysmal. Paroxysmal dyspnea associated with edema of the lungs, with or without cardiac pain, is to be differentiated from dyspnea of cerebral origin with the Biot type of respiration. Mackenzie¹⁷ believed that the paroxysmal type associated with heart disease was due to a lessened cardiac output. Pratt¹⁸ said that this

16 Sweeny, John A. Personal communication to the authors.

17 Mackenzie, J. Cardiac Asthma, Brit. M. J. 2 1231, 1911.

18 Pratt, J. H. Cardiac Asthma, J. A. M. A. 87 809 (Sept. 11) 1926.

type of dyspnea is never accompanied by failure on the right side, but originates in the left ventricle. It is usually not associated with valvulitis, but shows a tendency to develop anginal pain. Weiss¹⁹ believes that one important factor is increased blood load in the lungs due to change in the position of the body and the presence of disease of the lungs.

In the present series, five patients had the progressive type of congestive failure, one of them had paroxysmal dyspnea for a time. In the remaining case the congestive type of dyspnea was present at the onset of symptoms, but was later replaced by a paroxysmal type which dominated the clinical course during the last year. Histologic study revealed diffuse sclerosis of the intrinsic coronary vessels. We believe that disease of the smaller radicles of the intrinsic coronary system in the final distribution to the muscle fibers results in a lessened margin of physiologic function, and could be one of the basic factors in the pathologic physiology of the paroxysmal type of breathing.

Heart Sounds—Changes in the normal heart sounds are due to associated pathologic processes. The tendency in rheumatic valvulitis, as seen at autopsy, is toward healing with fibrosis and calcification leading to definite rigidity of the structure and a stenotic lesion. It is only in the rapidly progressive lesion in which the inflammatory element predominates over the tendency to heal that the lesion is essentially regurgitant. This applies to all the valves involved. On the other hand, in syphilis limited to the aortic system, there is definite retraction of the valve cusps, with shortening of the leaflets, smooth thickening and rolling back of the edges of the valve and a widening of the ring, due to commissural disease, a lesion resulting primarily in insufficiency. The valves are usually much softer and more leathery than the lesion resulting from rheumatic disease, and calcification, when present, is a much finer deposit and is well masked by the fibrosis.

The differential diagnosis of an aortic lesion rests largely between the rôle of rheumatic fever and that of syphilis. Sclerosis, with its varied etiology, must also be considered. Because of the predominance of stenosis in rheumatic aortic disease, the heart sounds are rougher and higher pitched, and there is a sharper differentiation between the systolic and the diastolic phase of the murmur. There is often a faint first sound that is muscular in quality, almost masked by the systolic murmur, an almost imperceptible midsystolic-diastolic pause and the diastolic murmur. In syphilis, on the other hand, the rolled back,

¹⁹ Weiss, Soma, and Robb, G. P. Cardiac Asthma (Paroxysmal Dyspnea) and the Syndrome of Left Ventricular Failure, *J. A. M. A.* **100**:1841 (June 10) 1933.

smooth edges give a soft blowing, low-pitched systolic murmur followed immediately by a low-pitched decrescendo murmur, the systolic phase is scarcely separated from the diastolic phase, making the "lub-tu" murmur characteristic of the aorta and aortic valves. Rarely, a deformed valve behaves like a vibrating reed in the blood stream, producing a high-pitched musical murmur approaching a sound which can be heard in the brachial and radial arteries, a mechanism produced only by the smooth fibrotic lesion of syphilis.

In the present series, in five of the six cases, there were harsh mitral stenotic murmurs with diastolic murmurs and an accompanying precordial thrill. In one case there was only a systolic murmur at the mitral valve, and in one a blowing systolic murmur at the aortic area. In another case there was a systolic murmur transmitted to the carotid arteries with a thrill over the vessels and a diastolic murmur; post-mortem examination revealed a rheumatic lesion of the aorta. The one case of aortic regurgitation diagnosed clinically as frank aortic regurgitation, syphilitic in origin, had no detectable first sound, but a loud blowing diastolic murmur transmitted down the border of the sternum. This man had markedly widened commissures and smooth rolled back cusps of the valves with thickened free valve flaps. The histologic examination revealed evidence of a marked syphilitic and an extremely active rheumatic lesion. The lesion was predominantly inflammatory, and definite conclusions as to the predominant etiologic factor could not be made.

Three patients of this series had a typical rheumatic fever of the subacute type, low grade, with periods of exacerbations. A low grade elevation of temperature usually in the neighborhood of 99 F was present in two others. In only one case was the temperature normal until the onset of lobar pneumonia, the rheumatic disease, although active in the pathologic sense, was not of sufficient intensity to produce the rise in temperature ordinarily associated with this, a subclinical infection.

Eyegrounds—Stokes²⁰ called attention to a symptomatology which is apparently rheumatic, but which on careful observation is that of syphilis in disguise. Rarely it may be difficult to determine the etiology of aortic valvular disease. The eyegrounds and reflexes may give valuable information as to the presence of neurosyphilis. One patient of this series had slightly irregular pupils, with a sluggish reaction to light and in accommodation. Of the remainder, two showed sclerotic vessels. Only one, therefore, had changes suggestive of syphilis.

²⁰ Stokes, J. Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926.

Serology—The Wassermann reactions of the blood in the entire series were consistently positive. In one case of secondary syphilis, the reaction became negative under therapy. We feel that repeatedly positive reactions are definite evidence of syphilitic infection, and that any case of rheumatic cardiac disease showing such results should be carefully studied to evaluate the rôle of syphilis as an added load.

Roentgenology—Based on six years' study of cases of syphilitic and rheumatic cardiac disease checked by autopsy, the following criteria were used in the differential diagnosis of syphilitic and rheumatic heart disease: (1) for rheumatic infection of the valves, (a) predominant enlargement of the left auricle, (b) early pulmonary stasis and widening of the pulmonary vessels, (c) enlargement of the right ventricle and (d) normal width of the aortic ring, (2) for syphilitic aortitis involving the aortic ring, (a) widening of the aortic ring (syphilis not involving the ring does not cause such widening), (b) enlargement of the left ventricle, (c) late engorgement of the pulmonary field after the onset of congestive failure and (d) late enlargement of the right ventricle dependent on right-sided failure and strain.

In our series, four patients revealed typical stenotic lesions of the mitral and aortic valves. In two, widening of the aortic ring developed under observation. One case remained of the regurgitant type, the pathologic process was strikingly inflammatory, with slight evidence of a tendency to heal. The remaining case presented several findings which offered difficulty in interpretation. Although the left auricle was enlarged to the degree compatible with a stenotic mitral orifice, the left ventricle was correspondingly disproportionately large. In the presence of an aortic ring of normal width and a prominent supraventricular aortic curve, the possibility of hypertension suggested itself. Renal histologic study revealed benign nephrosclerosis.

Five patients had the inspiratory type of heart seen in mitral stenosis, in the last case, that of aortic regurgitation, the heart was of the expiratory type.²¹ Table 3 summarizes the roentgen ray observations.

Electrocardiographic Study—The electrocardiographic records parallel certain changes in the normal functions of the heart due to disease and may give valuable information as to anatomic lesions, rate and rhythm. They do not determine the etiology, but may give confirmatory evidence of clinical diagnoses. Friedlander²² found that electrocardiographic records were not pathognomonic of rheumatism, syphilis or

21 Chandlee, G. J., and Burville-Holmes, E. Clinical and Roentgen Findings in the Study of the Heart and the Great Vessels, *Am J M Sc* **178**:304, 1929.

22 Friedlander, A. The Electrocardiogram in Luetic, Arteriosclerotic and Rheumatic Heart Disease, *Am Heart J* **5**:15, 1929.

TABLE 3—*Summary of Roentgenographic Observations*

Case	Left Ventricle	Left Auricle	Right Ventricle	Right Auricle	Aorta	Pulmonary Artery	Measurements				Type of Heart
							Left Branch, Cm	Right Branch, Cm	Base, Cm	Chest at Ninth Rib, Cm	
1	Marked enlargement	Marked enlargement, showing as double shadow on right side	Marked enlargement	Moderate enlargement	No sclerosis, no widening of base	Main branches not widened, are accentuated	10.0	11	10	21.5	Inspiratory
2	Enlarged	Similar to case 1	Enlarged	Moderate enlargement	No sclerosis, no widening of base	Main branches widened, marked enlargement of conus, shadow of cava to right of aorta	11.4	6.2	Cannot be measured	31.0	Inspiratory
3	Enlarged	Enlarged	Enlarged	Moderate enlargement	Widened, no widening of base	Main branches widened, marked signs of pulmonary fibrosis	11.5	11	5.5	27.0	Inspiratory
4	Moderate enlargement	Enlarged	Enlarged	Moderate enlargement	Slight sclerosis	Passive engorgement	9.3	5.8	7.2 (2d rib)	23.7	Inspiratory
5	Marked enlargement	Enlarged	Enlarged	Enlargement	Accentuated, ascending aortic curve	Main branches widened		Not available			Inspiratory
6	Greatest enlargement	Enlarged	Enlarged	Enlargement	Moderate widening, base widened	Main branches widened	11.0	5.2	5.5	29.5	Expiratory

arterial sclerosis in heart disease, but that the electrocardiograms in syphilis and arteriosclerosis showed a striking parallelism

The most striking feature in the electrocardiographic study in this series was the occurrence of auricular fibrillation in the cases showing the most extensive auricular disease. In one case auricular fibrillation developed under doses of digitalis considered within therapeutic limits, and promptly returned to normal rhythm after the administration of digitalis was discontinued. In the other case, with established auricular fibrillation, complete heart block with bundle branch block and a Q wave in lead 3 developed on treatment with digitalis and returned to auricular fibrillation after the drug was withdrawn. The direct chest leads showed one returning cycle of the dominant rhythm in this case. These observations suggest that active cardiac infection and disease render the heart more susceptible to the toxic effects of digitalis.

A rate of 100 or over was present at some time in five of the six cases. All but one (chronic auricular fibrillation) had an auriculo-ventricular conduction time of 0.2 second (top normal). Prolonged auriculoventricular conduction time is recognized as a frequent finding in rheumatic heart disease. The anatomic explanation possibly lies in an inflammatory lesion of the auricular wall extending upward from the mitral valve in the neighborhood of the portion of the conduction system lying between the auriculoventricular node and the bundle of His. The extent of the lesion in the auricular wall may likewise determine the liability to the development of auricular fibrillation.

Slurring was the most constant change in the QRS complex, being present in five of the six cases, and was evidence of myocardial disease. In one case there was marked notching in leads 2 and 3. A large Q wave appeared in lead 3 in one instance after auriculoventricular dissociation, and remained constant but of less amplitude on return to the dominant rhythm of auricular fibrillation. In another case a Q wave appeared, but subsequently disappeared, digitalis was not administered in this case.

A diphasic T wave was the change most commonly present. T waves were also found to be influenced by digitalis. The one exception was the case in which the T wave in lead 3 was always inverted. The T wave became more evident as the disease progressed. This was the case of marked progressive cardiac enlargement, with increasing right axis deviation and right ventricular hypertrophy. In one case, with marked notching of the QRS complex, a definite T wave found in coronary disease with a low take-off of the ST interval developed. Juster and Pardee²³ found this abnormality in patients with aortitis.

²³ Juster, I. R., and Pardee, H. E. B. Abnormal Electrocardiograms in Patients with Syphilitic Aortitis, *Am Heart J* 5: 84, 1929.

This case was of the regurgitant type, with an active syphilitic aortic valvular lesion and extreme stenosis of the mouths of the coronary arteries

TABLE 4—*Summary of Electrocardiographic Observations*

Case	Date	Rhythm*	Rate	A V Conduc- tion	Q R S	S T	Axis Devia- tion	Digitalis
1A	6/ 1/27	NS*	115	0 22	Slurring in leads 1, 2, 3	Upright T1 2 3	None	None
2B	1/31/27	NS	75	0 20	Slurring in leads 1, 2, 3	T1, T2 diphasic, T3 inverted	None	10 cc 1/26 to 1/31/28
C	4/ 5/23	NS	107	0 16 0 20	Slurring in leads 1, 2, 3	T1, T2 upright T3 inverted	Slight right	24 cc 2/1 to 3/26/28
D	5/ 8/28	AF†	80		Slurring in leads 1, 2, 3	T1 upright T2 diphasic, T3 inverted	Right	74 cc 4/10 to 5/8/28
E	6/21/28	NS	107	0 16 0 20	Slurring in leads 1, 2, 3	T1 upright, T2 diphasic, T3 inverted	Slight right	4 cc 5/16 to 6/7/28
3F	5/17/28	NS	90	0 20	Slight Q wave in lead 3	T3 diphasic	None	None
G	8/28/23	NS	88	0 20	Q wave absent in lead 3	T2 diphasic, T3 upright	Slight right	None
4H	1/ 9/28	NS	110	0 20	Slurring in leads 1, 2, 3	Low voltage	None	38 cc 12/27/27 to 1/3/28, before admission
5I	4/ 9/29	CAF‡	60		Slight slurring in leads 1, 2, 3	T1, T2, T3 diphasic	Tend- ency to right	None
Ja	6/11/29	CAF, A V disso §	40		Notching, slurring, widening in leads 1, 2, 3	T1 diphasic, T2, T3 inverted	Right	34 cc 5/31 to 6/11/29
Jb	6/13/29	CAF, A V disso §	40		Notching, slurring widening			Same as Ja
K	6/20/29	CAF	60		Slurring in leads 1, 2, 3, Q wave in lead 3	T1, T2 diphasic, T3 slightly inverted	None	None
L	8/26/29	CAF	80		Slurring in leads 1, 2, 3, Q wave smaller in lead 3	T1, T2 diphasic, T3 inverted	Slight right	12 cc 7/10 to 7/15/29, 17 cc 8/10 to 8/26/29
6M	8/19/30	NS	88	0 20	Slurring, slight notching in leads 1, 2, 3	ST comes off slightly below iso-electric level, T1 upright, T2, T3 diphasic	None	None
N	9/ 6/30	NS	100	0 20	Slurring in lead 1 widening in leads 2, 3	ST comes off slightly below iso electric level, T2, T3 coronary	Left	18 cc 8/9 to 9/6/30

* Normal sinus rhythm

† Auricular fibrillation

‡ Chronic auricular fibrillation

§ Auriculoventricular dissociation

Axis deviation, when present, usually tended to the right. The inspiratory type of heart was present in all these cases, as shown by roentgenographic study, and the majority presented tricuspid lesions. The only case of predominant regurgitant aortic insufficiency with the expiratory type of heart showed roentgenographically the development of an axis deviation to the left. The electrocardiographic observations are summarized in table 4.

SUMMARY

The study of the clinical course and pathologic changes in this series of six cases of combined syphilitic and rheumatic infection revealed that the predominant lesion was rheumatic. A stenotic lesion of the mitral valve occurred in four of the six cases. The remaining two cases had predominant insufficiency of the mitral valve from an extremely active inflammatory lesion. In five cases active rheumatic valvulitis involved the aorta, three times with stenosis and once with an incompetent valve. The incompetent valve had an extremely active rheumatic and an active syphilitic infection. In one case the aortic valve was normal, syphilitic aortitis was present above the valve, but it did not involve the ring. The evidence of syphilis was most pronounced in the commissural region and frequently limited to it. Syphilis of the myocardium could not be proved. Associated coronary disease of the small vessels complicated one case. One case showed aortitis involving the mouths of the coronary orifices.

The combined infection apparently occurs most frequently in the colored race, five of the six patients being Negroes, and it is likely to manifest itself during young adult life. The histories suggested that the rheumatic infection preceded the syphilis and was reactivated by it. The clinical course was rapidly progressive and usually typically rheumatic. One case of coronary sclerosis had the clinical course of coronary disease and not syphilis or rheumatic fever.

Pain was present in five of the six cases and was usually of the rheumatic infectious type. Dyspnea was usually of the congestive failure type. Paroxysmal dyspnea occurred in the case with coronary sclerosis. The heart sounds in rheumatic stenotic lesions tend to be rough and high-pitched. In the aortic region, even when complicated by regurgitation, the rough, high-pitched sounds seemed evidence of stenosis. In syphilis of the aortic valve with insufficiency, the heart sounds usually are lower pitched and softer, and the systolic-diastolic pause heard in stenosis of the valve is absent. The eyegrounds showed evidence of syphilis in one case. Two showed sclerotic changes, and the case in which the heart was never well compensated revealed marked engorgement of the veins. Serologic reactions were positive in all cases.

Roentgen examination revealed stenotic lesions of the mitral and aortic valves. Five of the hearts were of the inspiratory type, one with a predominant aortic lesion of regurgitation was of the expiratory type.

The most frequent findings in the electrocardiogram were tachycardia and from top normal to prolonged auriculoventricular conduction time. All but one case showed slurring of the QRS complex. Three showed a tendency to right axis deviation, only one to left axis deviation.

Two cases with most marked auricular disease showed a conspicuous toxic reaction to digitalis

CONCLUSIONS

1 The lesions and the clinical course in the six cases of combined syphilitic and rheumatic infection of the heart and great vessels were mainly rheumatic, in one case only was the rôle of syphilis of equal importance to that of rheumatic infection

2 The combined active infections carry a much graver prognosis than either infection occurring separately

3 Dyspnea of the coronary and congestive failure types must be clearly differentiated for the institution of correct therapeutic measures

4 Heart sounds help in the differential diagnosis of rheumatic and syphilitic aortic disease

5 Roentgenology is a valuable aid in the differential diagnosis between the rôles of syphilis and rheumatic infection in the production of cardiovascular pathologic processes

6 The electrocardiogram is of most value in studying the clinical course of disease and as a check on digitalis therapy

7 Study of the clinical characteristics of pain helps to differentiate more clearly the basic pathologic process associated with the various types of cardiovascular disease

Dr George Plehn made the roentgenographic studies of these cases. The observations are to be reported by him in greater detail in a separate communication.

SOME FACTORS DETERMINING THE VARIABILITY OF SKIN TEMPERATURE

H FREEMAN, M D
AND
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The application of the thermocouple has provided a new and exact technic for the determination of skin temperatures. The fineness of the instrument, however, has to a certain extent created a false impression as to the accuracy of the determinations. The inherent variability of the phenomena governing the level of the surface temperature has undergone little investigation, and its effect on the reliability of single determinations has been largely unchecked. In the present investigation an attempt was made to determine the magnitude of the variation to be expected in such a study.

METHOD

The investigation was conducted in a windowless, brick-lined, circular room, the temperature of which was maintained between 23 and 24 C and the air flow of which was so regulated as to be imperceptible to the nude subject. The relative humidity was measured at frequent intervals by a sling psychrometer. The subjects were male schizophrenic patients with no organic disease. The fact that the subjects were psychotic presumably has no significant bearing on the question at issue. They were studied under basal conditions, completely unclothed and lying on a bed containing a mattress covered with a sheet. The thermocouple was of the type utilized in the investigations of Benedict, Koropatchinsky and Finn¹ and could be read accurately to within 0.05 C (0.09 degree F). The various points on the skin selected for measurement are designated by numbers, and their location can be identified on the figure in chart 1.

The first investigation was undertaken to determine the time at which the skin temperature attained an equilibrium with the conditions of the test room so that the rest period might be of sufficient length to nullify differences in the previous environment. For this purpose, six patients were studied under fasting conditions. After a fifteen minute rest and every fifteen minutes thereafter over a total period of one and one-half hours, readings were taken at each of the seventeen points designated in chart 1.

From the research service of the Worcester State Hospital and the Memorial Foundation for Neuro-Endocrine Research

1 Benedict, F G, Koropatchinsky, and Finn, M D. Etude sur les mesures de température de la peau, J de physiol et de path gen 25 1, 1928

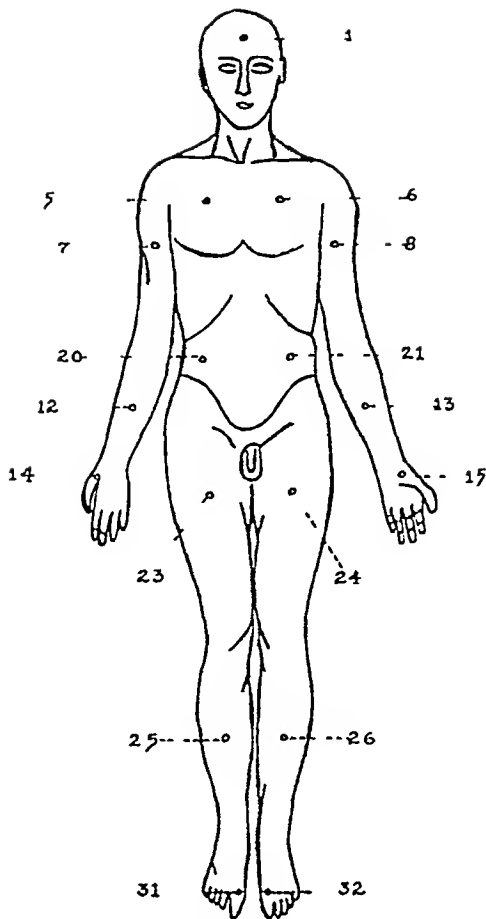


Chart 1—Topographic location of points studied

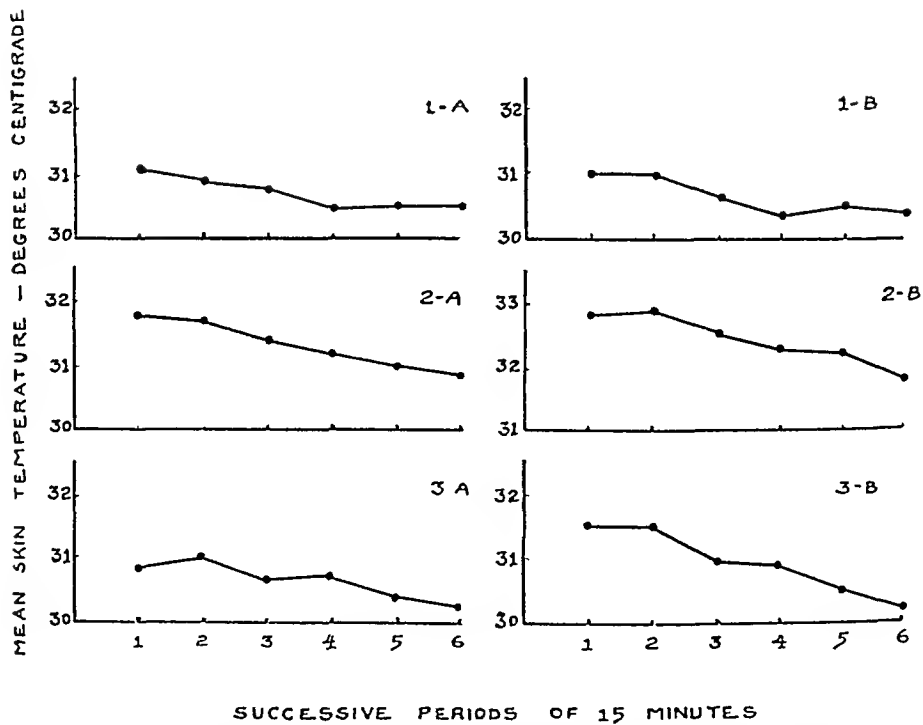


Chart 2—Means of skin temperature for six patients taken every fifteen minutes during a one and one-half hour period

RESULTS

The behavior of the subjects is illustrated in chart 2, in which is depicted the slope of the mean of the seventeen readings for each of the six patients. From the first reading there was a general fall in the temperature, which in four of the cases, at least, had not attained a resting level at the end of ninety minutes. Two of the patients had reached an apparent equilibrium at sixty minutes. It is evident, then, that in the majority of subjects a longer period than one and one-half hours is necessary to attain an equilibrium to environmental conditions such as were present in the test room. As there is an individual difference in the curves, a short rest period cannot be utilized in the supposition that the error in such a procedure would be a constant one.

Closer analysis of the figures reveals other features of interest. The subjects were studied in pairs, each two being subjected to the same

TABLE 1—*Drop in Skin Temperature During a One and One-Half Hour Interval**

Forehead (1)†	—0.17‡
Chest (5)	0.78
Abdomen (20)	0.93
Upper part of leg (23)	0.76
Upper part of arm (7)	1.22
Lower part of arm (12)	1.06
Lower part of leg (25)	0.69
Thumb (14)	1.61
Toe (31)	—0.24‡

* Values are expressed in degrees Centigrade.

† In this and the following tables the figures in parentheses are those used to indicate the various points on the body in chart 1.

‡ The minus sign indicates a rise in temperature.

pretest and the test conditions. The dominating influence of environment on the skin temperature is shown by the fact that if the first readings for the two members of each pair are compared a strong positive relationship is found, furthermore, if the last readings are similarly matched, apparently an equally good correlation is evident. As the fifteen minute reading is representative of the pretest conditions and the ninety minute period more indicative of the test environment, the equalizing effect of external factors on the skin temperature is evident. The sensitivity of the responsive mechanism is further shown by the greatest resemblance between the slopes for the members of each pair than between those for different pairs. For this reason, it seems desirable in any comparison of skin temperatures in normal or pathologic conditions to measure one person from each group simultaneously, so that errors due to environmental differences may be equalized and thus reduced in importance.

Despite the general tendency toward a continuous fall in skin temperature on recumbency, the process was not manifested uniformly

over the entire body In table 1 is a comparison of the total fall in temperature over the one and one-half hour period during which the various areas were studied In general the change was of greater extent in the peripheral than in the central points Over the forehead there was a slight rise in temperature On the thumbs there was a fall of over 1.5 C (2.7 F) The outstanding exception was in the case of the toes, in which a slight elevation of temperature occurred This may possibly have been due to the fact that the temperature of the toes was so low (25 C [77.4 F]) that it could fall no further under the given environmental conditions The more marked fluctuation in the extremities is in accordance with the greater rôle which they play in the adaptation of the surface temperature to environmental conditions² As it is the extremities which are of most interest in clinical studies of skin temperature, the error involved in not permitting a proper period of adjustment undoubtedly may be a factor leading to erroneous conclusions

A second phase of the investigation was the determination of the minute-to-minute variation in the temperature of the skin In any extensive study of surface temperatures, many readings must be made extending over a varying length of time At an environmental temperature of 23 C the organism undergoes a continuous loss of heat with a consequent reflection in the temperature of the skin Under such conditions any single reading is representative only of the state existing at the moment the reading was made, and it is consequently desirable, in making an exact study, to determine the amount of variation occurring over the period of the investigation

Accordingly, for eight patients, after a rest period of thirty minutes, repeated measurements were made over five points (1, 5, 12, 23 and 31 in chart 1) considered representative of various areas on the body In the case of the first two patients the readings were made in each area at intervals of one minute over a period of five minutes It was immediately evident, however, that a slight but consistent rise in temperature was present in the later readings While the exact cause of this trend was uncertain, it was considered to be due to a reflex vasodilatation from the irritant effect of the slight pressure or to a blanketing effect of the ebony support of the thermocouple during its ten second period of application To minimize the possible effect of this factor, the interval between measurements was increased to two minutes and the total period to ten minutes Despite this, however, the increase in temperature was still evident on the forehead (1), chest (5) and toe (31), as shown in table 2, but not on the lower part of the arm (12) or the upper part

² Maddock, W. G., and Collier, F. A. The Rôle of the Extremities in the Dissipation of Heat, *Am J Physiol* 106:589 (Dec) 1933

of the leg (23) This upward trend is more important as the previous investigation has shown that a fall in skin temperature would be expected during this period

The presence of this systematic tendency of the temperature to rise on repeated applications of the thermocouple somewhat complicates the analysis of the short time variation, but its evaluation may be aided by a study of the areas in which it did not occur In table 3 are enumerated the standard deviations of the variation occurring over these portions of the body surface On the lower part of the arm (12) and

TABLE 2—*Means of Surface Temperature Measurements on Six Patients at Consecutive Two Minute Intervals**

	First Minute	Third Minute	Fifth Minute	Seventh Minute	Ninth Minute
Forehead (1)	33 67	34 08	34 27	34 35	34 43
Chest (5)	32 60	32 72	32 87	32 95	32 99
Lower part of arm (12)	32 02	32 06	32 10	32 13	32 14
Upper part of leg (23)	32 18	32 12	32 11	32 11	32 09
Toe (31)	26 18	26 26	26 31	26 42	26 85

* Values are expressed in degrees Centigrade

TABLE 3—*Variation for Five Consecutive Readings at Two Minute Intervals in Six Patients**

	Standard Deviation
Forehead (1)	0 364
Chest (5)	0 200
Lower part of arm (12)	0 100
Upper part of leg (23)	0 075
Toe (31)	0 440

* Values are expressed in degrees Centigrade

the upper part of the leg (23), the variation over a ten minute period in the majority of instances was no greater than 0 1 C, (0 18 F), and it is possible that were this disturbing upward trend eliminated the expected change over the entire skin would be approximately of this extent Such a value, however, would imply a possible maximum variation of 0 5 C (0 9 F), an error of sensible proportions In view of this fact, in an extensive investigation it might be well to vary among the subjects the order in which the different regions are measured so that there might be no weighting of the values of any particular area In this way, the error arising under such conditions may be so distributed that its importance becomes negligible

Another possible source of variation lies in the selection of the points at which the temperature is to be determined In repeated studies on a single subject or in comparative studies on several subjects, a certain amount of error inevitably must be introduced in locating the points to

be investigated unless great care is taken to relate them to fixed anatomic landmarks. As this is extremely time-consuming, it was thought to be more practicable to determine the approximate variation existing within a small area surrounding a given point. Accordingly, in eight patients, the five points previously noted were marked, and around each one were selected four spots equidistant from each other and so placed as to be representative of a circle of a radius of $\frac{1}{2}$ inch (1.27 cm).

The investigation first disclosed that the systematic trend noted in the previous study was not evident, the variation of the peripheral from the central points being of an entirely random nature. In table 4 are summarized the constants of the distributions of the differences of the surrounding points from the central ones. The mean differences are small, but this is to be expected, because the variation is such as to result in a cancellation of the plus against the minus deviations. The

TABLE 4—*Constants of Distributions of Differences of Adjacent Points from Central Points in Eight Patients**

Point	Minimum	Maximum	Mean	Standard Deviation
Forehead (1)	−0.55	+0.30	−0.11	0.21
Chest (5)	−0.70	+0.25	−0.13	0.19
Lower part of arm (12)	−0.50	+1.10	+0.16	0.41
Upper part of leg (23)	−0.95	+0.50	−0.14	0.25
Toe (31)	−1.30	+0.05	−0.05	0.51

* Values are expressed in degrees Centigrade

body points in general show greater consistency around them than do the peripheral ones, in the latter case there is more opportunity for anatomic variation within the small area investigated. In the majority of instances these differences extended from 0.2 C (0.36 F) to 0.5 C, depending on the topographic location. The maximum errors, however, may be much greater, being over 1 C (1.8 F) on the toe, even in such a small series as the one studied. It is evident, therefore, that in any careful study of skin temperatures the utmost care should be taken to localize the desired point carefully, for a slight variation in placement may result in appreciable errors. It would perhaps be desirable to obtain several readings around a given point, the mean being taken as the typical value for that area, and in this way minimize the magnitude of the possible variation.

COMMENT

This brief study has revealed that the experimental errors in the determination of skin temperatures are somewhat larger than is ordinarily assumed. Differences in temperature of about 0.5 C are to be examined critically before any significance can be attached to them. It seems superfluous to make measurements to the fineness of which

the thermocouple is capable when the physiologic variation is ten times that of the instrument. The most important finding presented in this study is the slowness with which the skin comes into equilibrium with environmental conditions. In order to eliminate completely the effects of the pretest environment, the skin must be exposed under uniform conditions for several hours before accurate readings can be made. This seems to be an ideal practically impossible of attainment in clinical practice, for it necessitates the possession of a chamber in which temperature, humidity and rate of air flow can be controlled. Nevertheless, unless such a standard procedure is maintained, gross differences alone can be accepted as reliable.

SUMMARY

In a study of the inherent variation of the skin temperature in persons with no organic disease, it was found that

- 1 The skin does not adapt itself in the majority of cases to a given temperature for at least one and one-half hours, and for approximate equilibrium several hours are probably necessary.

- 2 The minute-to-minute variation in the skin temperature is usually of the nature of 0.1 C. over the entire body, but it may be as high as 0.5 C.

- 3 An error in the placement of the thermocouple of one-half inch from the desired point usually results in a change of from 0.2 to 0.5 C., but in the extremities the change may be as great as 1 C.

A TEST OF BLOOD FLOW TO AN EXTREMITY

ITS CLINICAL APPLICATIONS

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The number of vascular tests is legion. Boerhaave is quoted as crediting Jan Swammerdam with the construction of the first plethysmograph. Stephen Hales, the English clergyman, was the first to measure blood pressure by cannulating the carotid artery of a horse in 1733. During the period that followed, accurate measurements of blood pressure in animals were made, while this study in man remained virtually a sealed book. Then, in 1896, Riva-Rocci introduced the armlet method, which gave reliable results and accurate estimations of systolic pressure. A cuff of standard width was introduced which eliminated error, and later a complete description by Körtöff of the auscultatory changes assured exact diastolic as well as systolic readings¹. A few workers still favored the oscillatory determinations.

During the last ten years there has been renewed interest in the peripheral vascular diseases. New methods have been devised, and the problem has been approached afresh. Sensitive thermocouples were used by Lewis² to measure skin temperature, and the work of Brown,³ Scott⁴ and Simpson⁵ in thrombo-angitis obliterans must be mentioned. The thermocouple, admittedly accurate, is too liable to gross external error in its practical use. Changes in humidity, fluctuations of room temperature, wind currents, the amount of sweating and other factors

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From the Department of Medicine, Northwestern University, and the Cook County Hospital

1 MacWilliams, J. A. Blood Pressures in Man Under Normal and Pathologic Conditions, *Physiol Rev* 5 304, 1925

2 Lewis, Thomas. Observations upon the Reactions of the Vessels of the Human Skin to Cold, *Heart* 15 177, 1929

3 Brown, G. E., and Giffin, H. Z. Peripheral Arterial Disease in Polycythemia Vera, *Arch Int Med* 46 705 (Oct) 1930. Horton, B. T., and Brown, G. E. Thrombo-Angitis Obliterans Among Women, *Arch Int Med* 50 884 (Dec) 1932

4 Scott, W. J. M. Improved Electrothermal Instrument for Measuring Surface Temperature, *J A M A* 94 1897 (June 21) 1930

5 Simpson, S. L. Instrumental Methods in the Study of Peripheral Vascular Disease, *Am Heart J* 6 309, 1930

which are exceedingly difficult to control often vitiate readings. This shortcoming led Johnson⁶ and Scupham and Gilbert⁷ to favor a finger plethysmograph. The most ingenious device of their own invention gives simple accurate records of the pulse wave of the finger or toe. It also serves to differentiate between spastic and obstructive vascular lesions. The improved Pachon oscillometer was used extensively in France by Cawadias,⁸ and in America by Samuels,⁹ Kramer¹⁰ and Friedlander.¹¹

A different approach was the study by Lewis¹² of changes in the color of the skin. He added a full page of colored illustrations to his report to serve as a guide or index. In addition, he studied exhaustively the flush and vascular reactions to histamine.¹³ Later, de Takáts¹⁴ advocated histamine readings as an index of collateral circulation.

We have long been puzzled by the paradox of arteriosclerosis, in that although the blood pressure in an arm gradually increases, often to twice the value seen in health, yet the arm actually becomes smaller and atrophic. With this in mind, these experiments were devised to give, if possible, some quantitative expression of the progress of this disease.

All experiments were done at Cook County Hospital, in ward 15, on normal healthy men, medical students, interns and patients in the ward. Tracings were made from only three women (nurses).

METHOD

A small quiet room with a fairly even temperature of about 72 F (22 C) was found suitable for these tests. The subject was asked to elevate his hand above his head for a few minutes to insure a more complete emptying of the veins of the arm. An elastic 3 inch (7.6 cm) Martin bandage was wound tightly about the arm, beginning at the fingers and proceeding spirally upward to 2 inches

6 Johnson, C. A. Studies on Peripheral Vascular Phenomena, Surg., Gynec. & Obst. **55**:731, 1932.

7 Johnson, C. A., Scupham, G. W., and Gilbert, N. C. Observations on Peripheral Circulatory Changes Following Unilateral Cervical Ganglionectomy and Ramisection, Surg., Gynec. & Obst. **55**:737, 1932.

8 Cawadias, A. P. The Oscillometric Examination of Arterial Permeability, Brit. M. J. **1**:419 (March 5) 1927.

9 Samuels, S. The Value of Oscillometry in Study of Circulatory Disturbance of Extremities, J. A. M. A. **88**:1780 (June 4) 1927.

10 Kramer, D. W. Evaluation of Various Methods of Investigating the Circulation of the Lower Extremities, Am. J. M. Sc. **185**:402, 1933.

11 Friedlander, A. Studies in Oscillometry, Am. Heart J. **9**:212, 1933.

12 Lewis, Thomas. Standard Colours for Use in the Study of Vascular Reactions of the Human Skin, Heart **15**:1, 1929.

13 Lewis, T., and Grant, R. T. Vascular Reactions of the Skin to Injury, Heart **11**:209, 1924.

14 de Takáts, G. Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, Arch. Int. Med. **48**:769 (Nov.) 1931.

(5 cm) above the elbow. It was always applied with uniform and maximum tension, often by the same person. A tourniquet was applied $\frac{1}{2}$ inch (12 cm) above the Martin bandage, just as a surgeon prepares an arm for amputation. As soon as the tourniquet was locked, the thin rubber bandage was removed and the arm was lightly dusted with powder and inserted into the plethysmograph. This instrument was of the usual construction, having a long brass tube fitted with several outlets and a flexible rubber cuff. An automobile inner tube of the size that fit the patient's arm worked admirably. A small rubber tube connected one outlet with a water manometer, which recorded directly on a smoked drum. All other outlets of the plethysmograph were closed during the experiments. After four or five minutes of occlusion, during which time an adequate control tracing and base line were obtained, the tourniquet was quickly released. A rapid regular rise was seen in the graph, followed by a sustained plateau. The drum was then stopped, and the increased volume of the system was measured by aspirating air from a Y tube between the manometer and the plethysmograph. This was generally recorded in 20 cc quantities, but when there were small "reactions" it was marked in 10 cc amounts. A uniform speed of 15 cm per minute was maintained by the drum. Outlets were opened and the base line was verified. A small rubber band was snapped about the arm at the free margin of the cuff, and the arm was withdrawn from the plethysmograph. Total volume measurements of the arm were determined by the immersion method. Our brass cylinder was equipped with a small lead strip which was used as an indicator of the water level, serving in this dual capacity nicely.

In our early experiments, the type and the height of the curve were studied. Generally, with a large arm a large rise was seen, and a small arm gave a small curve, so this method was abandoned. To overcome this error, an expression of the amount of increased volume of a part after release of the compressed artery to a given unit of that extremity was sought. Let C represent the amount in cubic centimeters of increased volume of a part after the release of the tourniquet, and T the total volume of the part included in the plethysmograph. This simply resolves itself to $\frac{C}{T} \times 100$. Or, in other words, it is the percentage of the total compressibility of the vascularity of a part to that part.

RESULTS

Several tests were made on the same person (fig 1). They were performed at intervals of one-half hour, since it was believed that all disturbing influences from previous compression would be abolished during that time. Ratios of the two arms were practically identical in several tests (table 1). In a series of twenty-four normal men (free from vascular disease), the ratios were from 4.5 to 8.8. Age apparently did not influence this ratio. The youngest, aged 20, and the oldest, aged 74, had figures of 5.2 and 5.3, respectively. Only three women were included, and while this number is too small for critical study, it is odd that their average was 5.9, as compared to 6 for the men. Errors incident to the method are great, so the ratios should be expressed only in the nearest tenths. In this group of twenty-seven normal persons, the lowest value was 4.4, and we arbitrarily accepted this as the lowest limit of normal. Smaller values were considered pathologic.

A group of thirty-one persons constituted the abnormal series (table 2) Six persons with diabetes gave values ranging from 4.5 to 8, all within the normal scope (fig 2) Four of these cases were complicated by other disease two by thyrotoxicosis, one by hypertension and early arteriosclerosis and one by bronze diabetes Apparently, the additional pathologic condition was insufficient to disturb this ratio There

TABLE 1—Normal Values for the Arms

Case	Name	Sex	Age, Yrs	T Total Volume		C Compressed Volume		Ratio $\frac{C}{T} \times 100$	Diagnosis
				Right Arm	Left Arm	Right Arm	Left Arm		
1	S P	M	20	1,150		60		5.2	Epilepsy
2	T S	M	23	1,470		80		5.5	Gastritis
3	D S	M	24	1,675		95		5.7	Normal
4	G F	M	24	1,500		90		6.0	Normal
5	D W	M	25	1,700		90		5.3	Normal
6	C B	M	26	2,040		120		5.9	Psychoneurosis
7	H L	M	29	1,980		130		6.6	Normal
8	C E	M	29	1,790		80		4.5	Normal
9	J P	M	30	2,020		110		5.5	Amebiasis
10	J J	M	31	1,460		85		5.8	Multiple sclerosis
11	A T	M	34	1,890		130		6.9	Syphilis
12	J A	M	35	1,550		70		4.5	Unresolved pneumonia
13	P B	M	36	1,320		60		4.5	Arthritis
14	S T	M	37	1,460		80		5.4	Peptic ulcer
15	O E	M	37	1,360		80		5.9	Rheumatic fever
16	R R	M	46	1,550		90		6.0	Fibrous tuberculosis
17	A B	M	46	1,610		100		6.2	Neurasthenia
18	A M	M	49	1,460		120		8.2	Duodenal ulcer
19	J H	M	51	1,490	1,450	100	90	67/62	Argyria
20	M S	M	53	1,765	1,810	140	140	79/77	Arthritis
21	T W	M	63	1,580		140		8.8	Chronic alcoholism
22	S O	M	65	1,320		75		5.7	Arthritis
23	D L	M	73	1,640		80		4.8	Cholelithiasis
24	G R	M	74	1,490		80		5.3	Arthritis deformans
Mean average								6.05	
25	E L	F	27	1,140		80		7.0	Normal
26	M S	F	28	1,460		65		4.4	Normal
27	E F	F	33	1,020		70		6.7	Peptic ulcer
Mean average								5.93	
Average for group								5.99	

were four persons with carcinomas who had ratios of 2.5, 2.7, 4 and 5.6 In the first two, the emaciation and cachexia probably accounted for these low values Two patients with aortitis (fig 3) gave ratios of 2.8 and 3.8, while a youthful patient with hypertension also gave 3.8 A patient with a syphilitic hemiplegia on the left side had a ratio of 2.7 in the paralyzed arm, and 3.4 in the other one (fig 4)

Patients with nephritis gave low ratios except in one case, which showed a normal value In two patients with acute exacerbation of chronic glomerulonephritis, the figures were 3.6 and 3.8 (fig 5) while in two patients with long-standing cases of chronic nephritis they were 2.6 and 4.1 (fig 6) A patient with chronic interstitial nephritis, a high

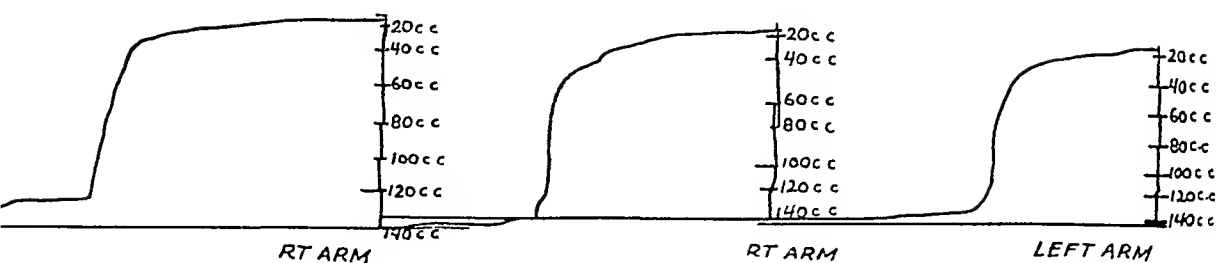


Fig 1—Tracings made on M S, aged 58, suffering from arthritis but free from vascular disease. The first two tracings were taken within one-half hour of each other, that of the left arm in the next half hour. The total volume of the right arm was 1,765 cc, the compressed volume, 140 cc. The total volume of the left arm was 1,810 cc, the compressed volume, 140 cc. The ratios were right arm, 7.9, left arm, 7.7.

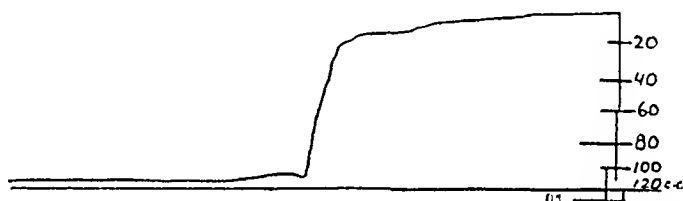


Fig 2—Tracing made on O H, aged 37, with diabetes, hypertension and early arteriosclerosis. The blood pressure was 180 systolic and 120 diastolic. The total volume of the arm was 1,935 cc, the compressed volume, 110 cc. The ratio was 5.7.



Fig 3—Tracing made on F P, aged 47, with aortitis and aortic regurgitation. The total volume of the arm was 1,280 cc, the compressed volume, 35 cc. The ratio was 3.8.

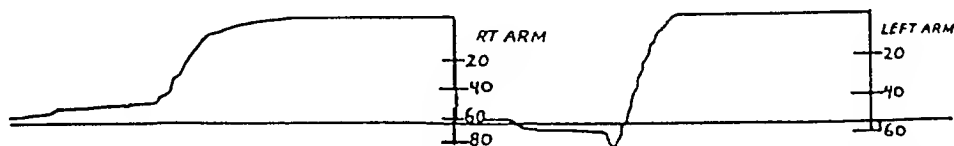


Fig 4—The first tracing was made on T A, aged 34, with syphilitic hemiplegia on the left. The first tracing is of the right arm, the total volume was 1,890 cc, the compressed volume, 65 cc, the ratio was 3.4. The second tracing is of the paralyzed arm, the total volume was 1,780 cc, the compressed volume, 50 cc, the ratio was 2.7.

grade hypertension and retinitis albuminurica had the lowest ratio of this group, 2.5

Patients with arteriosclerosis gave very low ratios, although there was one case that might be classed as normal. A markedly arteriosclerotic patient, aged 55 years, the youngest of these men, had a ratio

TABLE 2—Values for Different Diseased Conditions

Case	Name	Sex	Age, Yrs	T Total Volume		C Compressed Volume		Ratio $\frac{C}{T} \times 100$	Diagnosis
				Right Arm	Left Arm	Right Arm	Left Arm		
1	F H	M	24	1,980	1,775	100	80	51/45	Diabetes and thyroid disease
2	H J	M	25	1,510		120		80	Diabetes
3	R R	M	27	1,720		100		58	Diabetes and thyrotoxicosis
4	J W	M	29	1,900		110		58	Diabetes
5	O H	M	37	1,935		110		57	Diabetes and early arteriosclerosis
6	H N	M	52	2,150		90		42	Toxic adenomatoma
7	G P	M	65	1,420		65		45	Bronze diabetes
8	J W	M	48	1,950		110		56	Branchiogenic cancer
9	J B	M	53	1,480		60		40	Branchiogenic cancer
10	J S	M	61	1,460		40		27	Cancer of pylorus
11	N M	M	73	1,200		30		25	Cancer of rectum
12	F P	M	47	1,280		35		38	Aortitis and aortic regurgitation
13	W J	M	53	1,630		45		28	Aortitis
14	W G	M	15	1,420		55		38	Youthful hypertension
15	A V	M	48	1,360	1,340	75	85	55/63	Intermittent claudication
16	T A.	M	34	1,890	1,780	65	50	34/27	Left hemiplegia
17	B R	M	22	1,375		50		36	Acute exacerbation of chronic nephritis
18	J M	M	63	1,600		40		25	Retinitis albuminurica
19	T B	M	65	1,920		80		41	Chronic nephritis
20	P P	M	62	1,720		45		26	Chronic nephritis
21	W W	M	43	1,320		50		38	Acute exacerbation of chronic nephritis
22	W B	M	55	1,785		35		197	Marked arteriosclerosis
23	J S	M	53	1,400		40		29	Arteriosclerosis and sclerosis of coronary arteries
24	W K	M	58	2,080		60		29	Arteriosclerotic heart
25	H B	M	64	1,130		45		40	Arteriosclerotic heart
26	J F	M	64	1,525		45		30	Arteriosclerosis, diabetes
27	G B	M	65	1,810		80		44	Arteriosclerotic heart, decompensation
28	J H	M	76	1,440		50		35	Arteriosclerosis
				Right Leg	Left Leg	Right Leg	Left Leg		
29	H L	M	29	2,060		200		97	Normal
30	A V	M	48	2,060	2,000	130	90	63/45	Intermittent claudication
31	S O	M	53	2,520	2,560	130	120	51/47	Diabetes, arteriosclerosis, ulcers on both legs
32	E H	M	74	2,250		40		176	Dry gangrene on right leg

of 1.9. Three patients with arteriosclerotic hearts had ratios of 2.9, 3.5 and 4, and one whose condition was complicated by definite involvement of the coronary artery had 2.9 (fig. 7). A patient with diabetes and arteriosclerosis had a ratio of 3, while another with a decompensated heart had 4.4, a value that might be classed as normal. This group as a whole showed the most noticeable lowering of the ratio.

Tracings of the leg were made on only four persons, and these results are added since they indicate a similar change in the leg to that in the arm. A ratio of 97 (fig. 8) was found in a normal person, and one with an intermittent claudication (fig. 9) gave 4.5 and 6.3. This patient

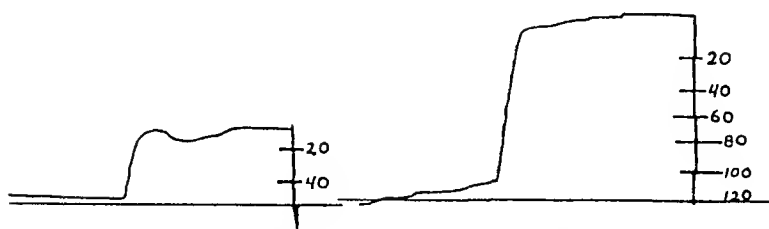


Fig 5—The first tracing was made on W W, aged 43, with acute exacerbation of a chronic glomerular nephritis, the total volume of the arm was 1,320 cc, the compressed volume, 50 cc, the ratio was 3.8. The second tracing was obtained on A M, aged 49, with a duodenal ulcer, the total volume of the arm was 1,460 cc, the compressed volume, 120 cc, the ratio was 8.2.



Fig 6—Tracing made on P P, aged 62, with chronic nephritis. The total volume of the arm was 1,720 cc, the compressed volume, 45 cc, the ratio was 2.6.

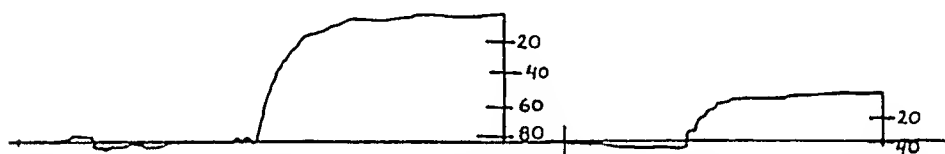


Fig 7—The first tracing was made on G R, aged 74, with arthritis, the total volume of the arm was 1,490 cc, the compressed volume, 80 cc, the ratio was 5.3. The second tracing was obtained on J S, aged 58, with coronary sclerosis, the total volume of the arm was 1,400 cc, the compressed volume, 40 cc, the ratio was 2.9.

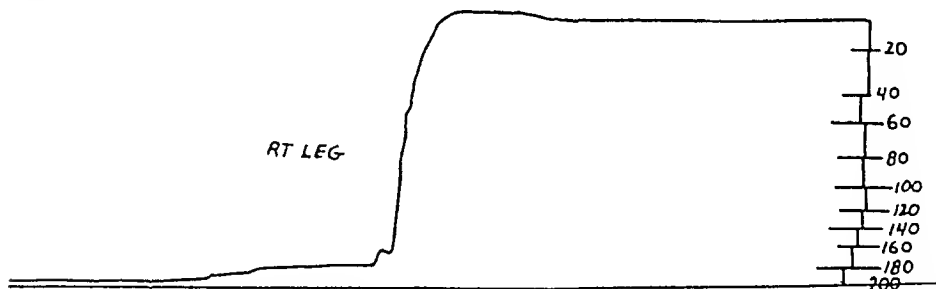


Fig 8—Tracing made on H L, aged 29, a normal subject. The total volume of the leg was 2,060 cc, the compressed volume, 200 cc. The ratio was 9.7.

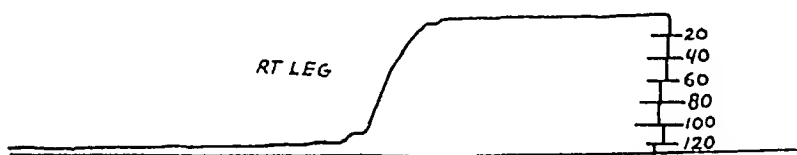


Fig 9—Tracing made on A V, aged 48, with intermittent claudication. The total volume of the leg was 2,060 cc, the compressed volume, 130 cc. The ratio was 6.3.

complained of more distress, clamps and pain in the left calf, the leg with the lower ratio. A patient with diabetes and ulcers on both legs, awaiting amputation, had a ratio of 5.1 and 4.7, and a patient with a self-amputating dry gangrene of the right great toe and arteriosclerosis gave only 1.7.

COMMENT

The method was critically examined by us, and all sources of error were appraised. First the Martin bandage was applied several times, and approximately the same increase in volume was noted. Several tests were made on the same subject on different days, and the error was within 20 cc. Second, the increase in air pressure was questioned as representing the increase in air volume. An arm was prepared in the usual way, then immersed in water, and the volume was noted. The tourniquet was then released, and the new volume was recorded. This increase roughly equaled the increase shown on a graph made later. Appreciation of the crudeness of the immersion method is necessary in evaluating these results. Third, many tracings had a small but gradual elevation during the control period. In earlier tracings, this was entirely eliminated by placing the left forearm in the plethysmograph prior to the experiment, thus warming it. As it was our object to have the rubber cuff fit as loosely as possible on the arm and cause no venous obstruction, many attempts were failures, as the cuff was not air-tight. To insure an air-tight system, this rise due to heat was welcomed as a check on the system, proper deductions of it were made later. Fourth, in some tracings, a depression and an irregular rise were displayed before the sustained high rise. They were movements of the arm in the plethysmograph incident to the removal of the tourniquet. Fifth, only a few patients showed muscular contractions of sufficient magnitude to interfere with the graph, but at no time did they obscure the levels. It must be added that our earliest attempts were disheartening, as they recorded all muscular movements, tremors and pulse waves. The instrument was made less sensitive, obliterating these curves and writing fairly regular curves which were easier to evaluate. Patients were seated with the arm in a horizontal position, the elbow properly supported and comfortably adjusted, so that most of them, even the very sick, had no difficulty in remaining quiet during the test.

Our results agree well with those of Hewlett and Van Zwaluwenburg,¹⁵ who studied the rate of blood flow to the arm following venous obstruction. Tschuewsky¹⁶ actually measured the blood flow to a dog's

¹⁵ Hewlett, A. W., and Van Zwaluwenburg, J. G. The Rate of Blood Flow in the Arm, *Heart* **1**:87, 1909.

¹⁶ Tschuewsky, J. A. Ueber Druck, Geschwindigkeit und Widerstand in der Strombahn der Arteria Carotis und Cruralis sowie in der Schilddrüse und in dem Musculus gracilis des Hundes, *Arch f d ges Physiol* **97** 210, 1903.

hindleg by a *Stomuh*. He found that after a brief arterial obstruction 6.89 cc of blood flowed per hundred cubic centimeters of leg. Sir Thomas Lewis, in his painstaking work on "reactive hyperemia," studied the effect of heat and cold, duration of obstruction and exercise on this phenomenon, but did not apply the test to any pathologic cases.¹⁷

Admitting from the outset the simplicity and crudeness of this apparatus, we believe this test is of value in the study of peripheral vascular disease. This paper is to be viewed only as a preliminary report, further work is now in progress.

CONCLUSIONS

- 1 A test of the total compressible vascularity of a part is described, and a ratio is used to express it.
- 2 Normal ratios vary from 4.4 to 8.8.
- 3 Ratios lower than 4.4 were considered pathologic.
- 4 Cases of diabetes, thyrotoxicosis, aortitis, hypertension, carcinoma, nephritis and arteriosclerosis were studied.

¹⁷ Lewis, T., and Grant, R. T. Observations on Reactive Hyperemia, *Heart* 12:73, 1925.

CIRCULATORY DYNAMICS IN MYOCARDIAL INFARCTION

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The clinical evidences of circulatory failure in the first days of myocardial infarction often differ conspicuously from the manifestations of decompensation in other diseases of the heart. In many instances the absence of orthopnea is striking, the patient evinces no distress when lying flat in bed despite the fact that grayish cyanosis and cold extremities testify to the impairment of the peripheral circulation. Moreover, inspection of the cervical and other superficial veins reveals that they are largely collapsed. These observations are in sharp contrast to those which one is accustomed to encounter when equally severe retardation of the peripheral circulation occurs in such conditions as, for example, mitral stenosis. In that case the patient is orthopneic, and the superficial veins are engorged. The picture in myocardial infarction is obviously the one which is familiar to every physician under the name of shock and which results from disturbances in the periphery of the circulation with a resultant decrease in the venous return to the heart. The remarkable feature is that this exquisitely peripheral type of failure results from myocardial infarction, a cardiac lesion *par excellence*.

In other instances of myocardial infarction the consequences of cardiac rather than peripheral circulatory failure are dominant. They may consist of manifestations of insufficiency of the left side of the heart, largely orthopnea and other consequences of pulmonary stasis, or the right side may fail, with resultant swelling of the systemic veins and of the liver. Most often, evidences of both cardiac and peripheral circulatory failure are present.

In this communication we present observations relevant to the nature of the derangements in the dynamics of the circulation underlying these diverse clinical pictures of myocardial infarction.

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* Eugene Meyer Fellow. Aided by a grant to the Emanuel Libman Fellowship Fund in memory of Adele Schiff.

** Emanuel Libman Fellow.

MATERIAL AND METHODS

Fifty-nine patients with clinical and electrocardiographic evidence of recent myocardial infarction were observed. Twenty-six cases were fatal and necropsy was performed in nineteen. In addition to the usual clinical observations, the venous pressure, circulation time and volume of the circulating blood were studied.

Venous Pressure—This was measured by the method of Taylor, Thomas and Schleiter,¹ with slight modifications.

The apparatus is an L-shaped glass tube 30 cm in length and 4 mm in bore. The short limb is ground to fit a 19 gage needle. The manometer is sterilized by boiling, and moistened with a 10 per cent solution of sodium citrate. The latter serves to inhibit coagulation during protracted measurements and minimizes the resistance to the flow of blood in the tube.

The patient is placed in the supine position. He is cautioned to relax and breathe as usual. The relaxed upper extremity is extended parallel to the mid-axillary line and propped up throughout its length by a pillow so that an ante-cubital vein is 5 cm below the anterior surface of the sternum at the attachment of the fourth rib. This is approximately the level of the caval openings in the right auricle.

The cuff of the sphygmomanometer is applied above the elbow and inflated to 30 or 40 mm of mercury. Immediately after insertion of the needle into the vein, the constricting cuff is deflated. The height attained by the column of blood in the tube is the venous pressure in centimeters of blood. A confirmatory reading is generally obtained by again inflating the cuff so that the blood in the tube rises above the level of the venous pressure. On releasing the cuff, the blood flows back into the vein until the column has fallen to the level of the venous pressure. The "blood up" and "blood down" readings should check closely.

In health, the pressure obtained by this method in a large antecubital vein is between 4 and 8 cm of blood.

Circulation Time—The method used was that of Fishberg, Hitzig and King.² Two and five-tenths grams of soluble glucose is dissolved by heating in 2 cc of sterile distilled water. It is taken up in a 5 cc syringe attached to a 19 gage needle and allowed to cool spontaneously to body temperature. The patient reclines in bed in a position which is as nearly flat as comfortable. He is instructed to relax and not to hold his breath following the insertion of the needle. He is also told that he will experience a sweet taste, which he should announce immediately. The arm is supported on a pillow as for the determination of the venous pressure. A tourniquet is applied just before the insertion of the needle into a large antecubital vein and removed as soon as the needle is in the vein. After waiting about a minute for any circulatory disturbance consequent on the venipuncture and application of the tourniquet to subside, the injection is performed as rapidly as feasible. The time elapsing between the injection and the perception of the sweet taste is recorded with a stop-watch. The subject usually describes the sweet taste as passing with great rapidity from the base to the tip of the tongue and quickly diminishing.

1 Taylor, F. A., Thomas, A. B., and Schleiter, H. G. Direct Method for Estimation of Venous Blood Pressure, *Proc Soc Exper Biol & Med* **27** 867 (May) 1930.

2 Fishberg, A. M., Hitzig, W. M., and King, F. H. Measurement of Circulation Time with Saccharin, *Proc Soc Exper Biol & Med* **30** 651 (Feb) 1933.

By this method, the circulation time in health is between nine and sixteen seconds. The circulation time thus determined is largely a measure of the velocity of blood flow through the lungs, for there is evidence to show that comparatively little time is taken for the blood to flow from the antecubital vein to the right side of the heart and from the left side of the heart to the capillaries of the tongue. The only complete capillary circuit traversed is that in the lungs. In accordance with this, we have found that great prolongation of the circulation time as tested by the gluside method is most common in failure of the left side of the heart with pulmonary engorgement. On the other hand, in the peripheral circulatory failure of shock, the time, when tested by gluside, is much less prolonged or even within normal limits.

The Volume of Circulating Blood—This was determined by the injection of congo red. The results in health are between 70 and 95 cc per kilogram of body weight.

The observations are recorded in table 1. The caption "duration of infarction" indicates the time between the onset of the first symptom that seemed definitely indicative of myocardial infarction and the time when the first circulatory measurements were carried out. This is only approximate, for in many instances the symptoms set in gradually. In the column headed "localization of fresh infarction," the site of the most recent infarction is described. The site of fresh infarction was determined at necropsy in nineteen cases.

In the remainder, the electrocardiographic criteria developed by Barnes and Whitten,³ Pardee and Bell,⁴ Crawford and his associates,⁵ Wilson and his co-workers,⁶ Fenichel and Kugell,⁷ and Wolferth and his associates⁸ were used to establish the general localization of the recent infarction. This electrocardiographic localization is expressed in the table as either anterior or posterior infarction. By anterior infarction is meant involvement of the anterior and apical portions of the left ventricle, which often extends far enough to the right to implicate the anterior third of the septum and the adjacent anterior and apical portion

3 Barnes, A. B., and Whitten, M. B. Study of the R T Interval in Myocardial Infarction, *Am Heart J* **5** 142 (Dec) 1929.

4 Pardee, H. E. B., and Bell, A. Report of Two Cases with Electrocardiographic Localization of the Thrombus in the Right or Left Coronary Arteries, *J A M A* **94** 1555 (May 17) 1930.

5 Crawford, J. H., Roberts, G. H., Abramson, D. I., and Cardwell, G. C. Localization of Experimental Ventricular Myocardial Lesions by the Electrocardiogram, *Am Heart J* **7** 627 (June) 1932.

6 Wilson, F. N., MacLeod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L. The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* **16** 155 (June) 1933.

7 Fenichel, N. M., and Kugell, V. H. Large Q-Wave of Electrocardiogram, *Am Heart J* **7** 235 (Dec) 1931.

8 Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C. Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads, *Arch Int Med* **52** 752 (Nov) 1933.

TABLE 1—Circulatory Measurements in Myocardial Infarction

Case	Duration of Infarction	Date	Venous Pressure, Cm of Blood	Circulation Time, Sec	Circulating Blood Volume, Cc / Kg	Arterial Pressure, Mm Hg	Localization of Fresh Infarction	Outcome
1*	5½ hrs	7/17	9	19½	101	110/ 80	Posterior (eeg †)	
		7/26	8			110/ 74		
		7/31	6	17	105	114/ 70		
		8/ 4	6	15½		112/ 70		Improved
2	18 hrs	3/10	10.5	18½		140/ 96	Equivocal (eeg)	
		3/11	5.5		82	120/ 96		
		3/12	8.5	17		110/ 80		
		3/13	7.5			130/100		
		3/16	8.5	20½		130/ 86		
		3/23	6.5	10¼		148/110		
		3/23	8.5	16¼		114/ 86		
		4/11	6.5	16½		98/ 78		
		4/20	6.5	15¾		118/ 90		Improved
Readmission		10/ 7	13	20	104	104/ 88		
		10/17	15	27		110/ 80		
		10/24	8.5	23		110/ 80		Improved
3	1 day	6/ 5	3.5			112/ 70	Anterior (eeg)	
		6/13	9.5			104/ 68		
		6/24	7			98/ 64		Improved
4	1 day	11/25	12.5	25		96/ 70	Posterior (eeg)	
		11/26	8	28	94	102/ 76		
		12/ 6	8	29		100/ 58		Improved
5	2 days	12/16	2.5	21	56	96/ 54	Equivocal (eeg)	
		12/19	6.5			92/ 54		
		1/ 2	5.5			88/ 52		Improved
Follow up		5/ 3	7	14½		148/ 90		No symptoms
6	2 days	6/ 8	5.5	14¼		110/ 84	Anterior (eeg)	
		6/14	5.5	13½		112/ 90		Improved
7	3 days	11/ 1	12	41	65	80/ 60	Myomalacia of anterolateral, septal, apical and basal portions of left ventricle, postmortem	Died, post mortem
8	6 days	7/30	1.5			140/ 84	Equivocal (eeg)	
		8/ 2	2			140/ 86		
		8/ 4	5			142/ 80		
		8/ 6	1.3			116/ 62		
		8/ 6	4.5			124/ 72		
		8/ 8	5			122/ 86		
		8/18	4			102/ 70		
		8/26	5.5			140/ 80		
		9/ 6	6			144/ 84		Improved
9	6 days	11/22	2.5	11½	70	122/ 80	Anterior (eeg)	Died, no autopsy
		11/26	3	11¾	73	114/ 76		
10	6 days	2/ 8	3.5	32	72	130/100	Anterior (eeg)	
		2/ 9	2.5			128/ 92		
		2/11	7.75	24		110/ 80		
		2/16	5			125/ 90		
		2/19	4			120/ 86		
		2/21	2.5			126/ 90		
		2/23	5.5					
		2/27	8		85	110/ 90		
		3/ 4	4.5	18¼		126/ 90		
		3/12	3	22		120/ 94		
		3/16	4.5			118/ 90		
		3/23	5	19¼		128/ 96		
		4/25	6	18		132/ 96		
		5/12	7	23		130/ 94		
Readmission		6/27	6.5	29	102	126/ 90	Anterior (eeg)	Improved
Readmission		11/ 6	10	39	110	146/104		Improved
11	7 days	11/17	2.5			100/ 68	Posterior (eeg)	
		11/20	3			112/ 68		
		11/24	3.25			100/ 60		
		11/27	2.5			114/ 60		Improved

* Cases 1 to 16 inclusive were instances of initial myocardial infarction, while in cases 17 to 59 inclusive there was notable cardiac insufficiency prior to the present infarction

† Electrocardiogram

TABLE 1—Circulatory Measurements in Myocardial Infarction—Continued

Case	Duration of Infarction	Date	Venous Pressure, Cm of Blood	Circulation Time, Sec	Circulating Blood Volume, Cc / Kg	Arterial Pressure, Mm Hg	Localization of Fresh Infarction	Outcome
12	9 days	12/22 12/25	18 22.5		90	142/ 90 96/ 72	Myomalacia of apex, both papillary muscles and lower portion of septum of left ventricle, perforation of septum	Died, autopsy
13	11 days	4/24 5/ 5	6 5.5	10½ 11		220/110 168/ 98	Posterior (eeg)	Improved
14	14 days	7/ 8 7/18 7/20 8/16	2 1 2 4.5	18½ 19½ 16	49 73	118/ 80 160/110 176/110 116/ 84	Anterior (eeg)	Improved
15	1 to 8 weeks	2/27 3/ 3	6 5	18½ 19		120/ 80 102/ 76	Anterior (eeg)	Improved
16	8 weeks (repeated attacks)	8/26 8/29 9/ 4	3.5 4 3.5			98/ 74 106/ 78 96/ 72	Anterior and apical portion of left ventricle	Died, autopsy
17	15 hours	6/ 6 6/10	3.5 6	14	32	96/ 70 130/ 94	Equivocal (eeg)	Improved
18	1 day	5/20 5/25 5/29 5/31	8.5 8 49 6.5	42 49 36		200/140 180/130 178/ 98	Posterior (eeg)	Improved
Readmission	7 days	7/26	20			136/ 80		Died, no autopsy
19	1 day	6/ 7	2.5			96/ 76	Posterior basal portion of left ventricle	Died, autopsy
20	1 day	10/6/32 10/ 7 10/ 7 11/28/33 11/29	2 6.5 4 20 18.5			130/ 88 160/106 210/140 184/118 168/108	Posterior (eeg)	Improved
Readmission				42	105			In hospital
21	1 day	9/27 9/30 10/ 3 10/10	8.5 11 8 6			150/ 92 180/110 160/ 90 146/ 84	Posterior (eeg)	Died, no autopsy
22	1 day	7/ 7 7/ 8 7/18	3 4.5 9.5	19 13½	94	112/ 88 98/ 70 120/ 90	Posterior (eeg)	Improved
23	1 day	5/30 6/ 9	10.5 6	23¾ 18½		174/ 94 172/ 80	Posterior (eeg)	Improved, died 4 mos later
24	1 day	10/ 4 10/ 6	5 6		68	106/ 80 92/ 76	Anterior (eeg)	Improved
25	1 day	8/25 8/26 8/28 8/31 9/ 1 9/ 2 9/ 4 9/ 6	12.5 9.5 6.5 4 3 3.25 3.5 3.5			90/ 60 96/ 70 102/ 70 86/ 56 94/ 56 96/ 56 104/ 60 96/ 60	Anterior (eeg)	Improved
26	1 day	4/17	19			170/130	Posterior basal portion and septum of left ventricle	Died, autopsy
27	1 day	7/22 8/17	17.5 4.5	29 15		120/ 80 146/ 86	Posterior (eeg)	Improved
28	1 day	10/28 10/29 10/30 10/31 11/ 3 11/ 6 11/ 9 11/10 11/14 11/21 11/24	10 7.5 4.5 6.75 8 9.5 8.75 7 6 7.5 6.25			120/ 90 106/ 80 94/ 78 104/ 78 92/ 72 104/ 84 110/ 84 114/ 92 106/ 90 110/ 90 124/ 94	Anterior (eeg)	Improved

TABLE 1—Circulatory Measurements in Myocardial Infarction—Continued

Case	Duration of Infarction	Date	Venous Pressure, Cm of Blood	Circulation Time, Sec	Circulating Blood Volume, Cc / K_2	Arterial Pressure, Mm Hg	Localization of Fresh Infarction	Outcome
29	2 days	4/18	3	16½		122/ 74	Equivocal (eeg)	Unimproved discharged against advice
30	2 days	12/30 1/ 1 1/11 2/ 3	8 10 8.5 7		98	118/ 76 124/ 80 108/ 72 80/ 56	Posterior (eeg)	Unimproved, psychotic transferred
31	2 days	0/25	4.5	32		125/ 85	Anterior and apical portions of left ventricle, anterior and apical portions of right ventricle	Died, autopsy
32	3 weeks	1/11 1/14 1/16	3 4 4			110/ 70 112/ 72 170/ 90	Liquivocal (eeg)	Improved
Readmission	2 days	8/ 0 8/10 8/13 8/21 8/28 9/ 5	12 16 8.5 9 7 8.5	27¼ 30 26 30	77	80/ ? 82/ ? 120/ ? 100/ ? 102/ ? 106/ ?	Anterior apical and septal portions of left ventricle	Died, autopsy
33	2 days	8/21 8/26 8/30	3 2.5 3.5	33½ 30 32	120	140/100 120/ 80 110/ 76	Liquivocal (eeg)	Died, no autopsy
34	2 days	4/ 4 4/ 6	10.5 13.5	45½	114	150/130 130/100	Liquivocal (eeg)	Died, no autopsy
35	3 days	11/22 11/23	15.5 15.75		96	86/ ? 80/ ?	Posterior basal portion and septum of left ventricle	Died, autopsy
36	3 days	4/14 4/15	14 19	36		80/ 56 78/ 52	Posterior, basal, posterolateral, anterior apical and anterolateral portions of left ventricle	Died, autopsy
37	3 days	8/17 8/18 8/20 8/21 8/22 8/24 8/25 8/27 8/28	2.5 5 3 2.5 3.5 2 3 2.5 4.5			118/ 64 130/ 56 134/ 68 114/ 60 130/ 66 120/ 62 130/ 66 132/ 76 130/ 74	Posterior (eeg)	Improved
38	4 days	2/ 4 2/ 6 2/ 7 2/ 8 2/13 2/17 11/29	3 4.5 1.5 3 6.5 5.5 6.5	21 22 36 21½ 38	92	130/ 90 108/ 80 108/ 76 114/ 88 150/100	Equivocal (eeg)	Improved in hospital
39	4 days	5/15 5/17 5/18	6 5.5 12	29 34	75	92/ 76 70/ ? 70/ ?	Posterior (eeg)	Died, no autopsy
40	4 days	3/31 4/ 8	6 6.5	13½ 14	98	110/ 70 116/ 82	Equivocal (eeg)	Improved
41	4 days	4/13 4/18 4/21 4/26 5/28	8.5 8 5.5 7.5 12	40 39 42 35¾	108	118/ 64 100/ 60 150/ 98 90/ 56 114/ 70	Anterior apical and septal portions of left ventricle	Died, autopsy

TABLE 1—Circulatory Measurements in Myocardial Infarction—Continued

Case	Duration of Infarction	Date	Venous Pressure, Cm of Blood	Circulation Time, Sec	Circulating Blood Volume, Cc / Kg	Arterial Pressure, Mm Hg	Localization of Fresh Infarction	Outcome
42	4 days	8/ 4 8/ 6	2 5 5 5			90/ 64 86/ 62		Improved
	Readmission 10 days	9/12 9/13 9/14 9/15 9/16	18 20 5 4 2 5			104/ 88 104/ 88 118/ 70 104/ 74 102/ 70	Posterior basal and septal portions of left ventricle	Died, autopsy
43	5 days	12/ 9 12/11	16 14 5			96/ 70 86/ ?	Anterior apical and septal portions of left ventricle	Died, autopsy
44	5 days	8/31 9/ 1 9/ 2	2 5 2 3 5		81	140/ 94 126/ 90 126/ 80	Posterior (eeg)	Died, no autopsy
	Fresh infarction	9/ 4 9/ 4 9/ 5 9/ 6	12 11 5 13 15 5			78/ 60 88/ 68 88/ 72 80/ ?		
45	6 days	11/22 11/27	4 6	23		110/ 80 130/ 84	Posterior (eeg)	Improved
46	6 days	11/28 11/30 12/ 2 12/ 6 12/12 12/17 1/ 3 1/ 5	9 5 9 8 5 15 5 9 11 9 5 9 5		114	92/ 76 100/ 80 88/ ? 118/ 90 112/ 80 108/ 86 86/ 56 108/ 80	Posterior basal, anterolateral, and anterior portions of left ventricle	Died, autopsy
47	7 days	8/ 7 8/10 8/15	2 4 5			84/ 58 106/ 64 90/ 62	Posterior (eeg)	Improved
48	8 days	4/26 4/27	19 17	31	113	178/114 172/110	Posterior basal portion of left ventricle and septum	Died, autopsy
49	9 days	2/ 7 2/ 9 4/ 4	3 5 6 5 7 5	51¾ 60½ 39	127	132/ 90 156/ 94	Posterior (eeg)	Improved, does light work
50	2 weeks	8/12 8/20	3 5 4 5	16¾ 13	114	86/ 66 86/ 60	Posterior (eeg)	Improved
51	2 weeks	3/28 4/ 8	7 8	11¾ 12	118	126/ 96 120/ 86	Equivocal (eeg)	Improved
52	2 weeks	4/10	26			192/110	Anterior, posterior apical and septal portions of left ventricle	Died, autopsy
53	2 weeks	8/20	11 5			120/ 68	Posterior, basal, septal and both papillary muscle portions of left ventricle	Died, autopsy
54	3 weeks	6/10	7 5	15		164/120	Posterior (eeg)	Improved
55	3 weeks	12/22 12/23 12/29 12/30	17 12 5 5 6			160/100 110/ 80 140/ 94 120/ 80	Posterior basal and anterior apical portions of left ventricle	Died, autopsy
56	3 weeks	7/23 8/ 9	7 25 7 5			128/ 82 142/ 96	Equivocal (eeg)	Improved
57	4 weeks	7/26 7/29 8/15	7 5 8 5 8 5	35½ 37 36	111	120/ 90 110/ 80 120/100	Anterior apical portion of left ventricle	Died, autopsy
58	4 weeks	4/21 5/25 6/22 7/20 7/26	23 5 25 5 17 5 20 19	47 34¾ 39 37 36	122	194/104 190/140 200/114 186/110 170/ 80	Posterior (eeg)	Improved
59	3 months	1/17 1/18 1/23	19 5 19 14			140/110 170/112	Anterolateral portion of right ventricle near base	Died, autopsy

of the right ventricle (T_1 type of Parkinson and Bedford,⁹ Q_1T_1 type of Wilson and his associates⁶ due to thrombosis along the left coronary system) By posterior infarction is meant a lesion of the posterior and basal portion of the left ventricle, which often also involves the posterior two thirds of the interventricular septum and the adjacent posterior portion of the right ventricle (T_3 type of Parkinson and Bedford, Q_3T_3 type of Wilson,⁶ usually due to thrombosis along the right coronary system) The electrocardiographic criteria seemed adequate for such general localization in thirty-one of the forty cases that did not come to postmortem examination

VENOUS PRESSURE

The venous pressure was measured in all the patients In most instances, repeated measurements were carried out, and in some the opportunity was afforded of studying the venous pressure during subsequent admissions

TABLE 2—*Venous Pressure in Myocardial Infarction*

Venous Pressure, Cm of Blood	Initial Infarction		Previous Infarction or Severe Heart Failure	
	Cases	Deaths	Cases	Deaths
Less than 4	8	2	11	3
4 to 8	5	0	16	6
More than 8	3	2	16	13 •

As is seen in table 1, the venous pressure in myocardial infarction varies from subnormal levels to as high as 26 cm It will be shown later that in the last analysis the height of the venous pressure in myocardial infarction is determined by whether shock or heart failure is predominant in the particular case Early in the investigation it became evident that the previous functional capacity of the heart is one of the main factors determining which of these is predominant The venous pressure was most often subnormal in what may be termed initial myocardial infarction, i e, cases which do not present a history of antecedent myocardial infarction and in which the patient has not previously been incapacitated by heart failure, although there may have been anginal pains or dyspnea on exertion as manifestations of the underlying coronary arteriosclerosis On the other hand, venous pressure was most often elevated or normal in myocardial infarction affecting persons who had previous similar episodes or who were suffering from severe heart failure prior to the present attack This is illustrated in table 2, which shows the venous pressure on the first measurement in our fifty-nine patients

9 Parkinson, J, and Bedford, D E Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* **14** 195, 1928

In Initial Myocardial Infarction—The venous pressure was subnormal in eight of the sixteen patients with initial myocardial infarction. In only three was it above the upper limit of normal. It is significant that in each of these three patients with high venous pressure in initial infarction, the interventricular septum was involved. In case 12, perforation of the septum had occurred, in case 7, complete heart block developed, and in case 4, septal involvement was revealed by prolongation of the auriculoventricular conduction time to 0.27 second.

Comparison of the venous pressure with the other clinical findings revealed that, as might be anticipated, low venous pressure is encountered especially in patients who present the clinical picture of shock. Venous hypotension is predominantly a feature of the early phases of myocardial infarction. In most cases, as the other manifestations of shock clear up, the veins can be seen to fill, and the pressure within rises to normal or elevated levels. This is the usual sequence of events in initial myocardial infarction that pursues a favorable course, and may be illustrated by a typical case.

CASE 22—A man of 48 years was admitted, with the history of suffering from precordial pain and dyspnea on exertion for about a year. On the morning of the day of admission, while at work he was suddenly seized with an extremely severe pain in the left side of the chest anteriorly and posteriorly which radiated to the left axilla and shoulder. The pain continued for several hours, with accompanying weakness, chilliness, sweating and a sense of impending death.

On admission, the patient was able to lie flat in bed. He was cyanotic, but not notably dyspneic, breathing eighteen times per minute. While the superficial veins of the neck and upper extremities could be seen, they were collapsed, and did not fill out when strong pressure was exerted on the right upper quadrant. The temperature was 98 F, but soon rose to 101 F. Gallop rhythm was audible at the apex. Neither basal second sound was accentuated, that at the pulmonic area being weaker than that at the aortic area. A few fine râles were audible at the left base posteriorly. The electrocardiogram revealed evidence of recent infarction of the posterior portion of the left ventricle. The R-T interval was elevated above the base-line in the third lead and slightly in the second lead, the T wave was inverted in the second and third leads and there was a large, broad Q wave in the second and third leads. Circulatory measurements were: arterial pressure, 98 systolic and 70 diastolic, venous pressure, 3 cm of blood, circulation time, 19.5 seconds.

The patient improved steadily, the manifestations of shock disappearing in a few days. Two days after admission, the venous pressure was 4.5 cm. Twelve days after admission, the circulatory measurements were: arterial pressure, 120 systolic and 90 diastolic, venous pressure, 9.5 cm of blood, circulation time, 13.5 seconds, volume of circulating blood, 94 cc per kilogram of body weight.

At this time, it could be seen that the cervical veins were much better filled than on admission, and swelled further during pressure on the right upper quadrant. Reference to the figures cited shows that as the patient came out of shock the venous pressure mounted parallel to a rise in arterial pressure and an acceleration in the velocity of blood flow. Indeed, the venous pressure of 9.5 cm is somewhat above normal, and is indicative of myocardial weakness due to the infarction.

It is a common sequence of events to find the venous pressure low, under 4 cm, when the patient enters the hospital in the early stages of infarction with the clinical picture of shock, and then as the shock passes away to observe that with the appearance of such manifestations of heart failure as orthopnea or swelling of the liver, the venous pressure rises to levels above the normal

However, there are also instances of myocardial infarction in which venous hypotension persists for weeks. In such patients, there is also persistence of other manifestations of shock. Usually, but not invariably, the precordial pain and its radiations continue at least intermittently throughout this stage, and fever, leukocytosis and the electrocardiographic findings testify to the parallel prolongation of the myocardial necrosis. This course of events was well illustrated in case 10.

In Patients with Previous Infarction or Heart Failure—The effect of myocardial infarction on venous pressure is usually quite different in patients who have had previous episodes of myocardial infarction or who are already incapacitated by severe heart failure due to the underlying coronary arteriosclerosis. In them, fresh infarction is more often documented by high than by low venous pressure. Of forty-three such patients, eleven had subnormal venous pressure, while in sixteen the venous pressure was above the upper limit of normal. The cases with low venous pressure were those in which the clinical picture was entirely dominated by shock. On the other hand, the more frequent cases with normal or high venous pressure presented predominantly the symptoms and signs of heart failure. Venous hypertension is especially apt to develop in patients who have had severe episodes of infarction, even though these antecedent infarctions were marked by subnormal venous pressure. In such cases, fresh coronary thrombosis with myocardial infarction may be documented by a rise in venous pressure to 20 cm (cases 18 and 20).

Two circumstances are especially apt to be accompanied by high venous pressure

(a) The first is extensive implication of the septum by the infarct. The postmortem examination in our cases with venous pressure of 20 cm or higher revealed extensive infarction of the septum. The three cases in which initial infarction was accompanied by high venous pressure were all instances of septal infarction. However, even massive infarction of the septum is not invariably manifested by a rise in venous pressure. In several of our cases infarction of the septum was accompanied by low venous tension, the depressing effect of the shock on the venous pressure outweighed that of the cardiac weakness.

(b) The second circumstance causing rise in venous pressure is certain disturbances in rhythm resulting from infarction, notably auricular

fibrillation, nodal rhythm, heart block or ventricular tachycardia. All these were exemplified in our series. But it should be borne in mind that these arrhythmias, except perhaps ventricular tachycardia, are especially apt to occur on the basis of septal infarction, which is per se apt to raise the venous pressure. But the arrhythmia will tend to elevate the venous tension to the extent that it impairs the functional capacity of the right side of the heart.

However, the depressing effect of such changes in rhythm on the functional capacity of the heart does not always suffice to overcome the effect of the shock, which is generally pronounced in these cases, and we have encountered low venous pressure during ventricular tachycardia due to myocardial infarction.

CIRCULATION TIME

The circulation time was measured in thirty-eight patients, in most on repeated occasions. The initial measurements afforded the results shown in table three.

TABLE 3—*Circulation Time in Myocardial Infarction*

Circulation Time, Seconds	Cases	Deaths
Less than 16½ (normal)	9	1
17 to 19½	6	0
20 to 29½	9	2
30 to 39½	8	5
40 or more	6	4

From the figures given in table 3 it is evident that in myocardial infarction the circulation time as estimated by the gluside method varies in different cases from normal values to very slow ones. How marked a retardation of the blood flow is represented by the slower rates given in the table will be clear if it is called to mind that a circulation time of forty seconds is about triple the mean normal.

There is no strict parallelism between the circulation time as estimated by the gluside method and the severity of the clinical picture of myocardial infarction. Despite severe and protracted pain, fever, leukocytosis, pericardial rub, gallop rhythm and the characteristic electrocardiographic changes of acute myocardial infarction, there may be comparatively little slowing of the blood flow as measured by the gluside method. Particularly significant is the fact that the patient may present the classic picture of shock and yet the circulation time by the gluside method reveals but slight, if any, slowing of the velocity of blood flow through the lungs. This is well illustrated in one of our cases.

CASE 5—A man of 48 years was admitted because of constricting substernal pain of two days' duration. After several hours, a fever of 102 F developed and he had chilly sensations. On admission, the patient's face had a grayish

pallor, while the lips and finger-nail beds were cyanotic, the hands and feet felt cold despite a rectal temperature of 102 F, and the skin was moist. He lay flat on one pillow without orthopnea or apparent dyspnea, breathing only twenty times per minute. The heart rate was 86, and a presystolic gallop rhythm was heard. Physical examination of the lungs revealed no abnormalities. The electrocardiogram revealed very low voltage, inversion of T_1 and T_2 , and a slight elevation of the R-T interval in the second lead. Circulatory measurements were: arterial pressure, 96 systolic and 54 diastolic, venous pressure, 2.5 cm of blood, circulation time, twenty-one seconds, and volume of the circulating blood, 56 cc per kilogram of body weight.

The patient thus presented the classic picture of circulatory shock due to myocardial infarction, with low venous and arterial pressures and subnormal volume of the circulating blood. That the arterial pressure was depressed was proved by the fact that ten months later it was 140 systolic and 80 diastolic. Nevertheless, despite all the evidence of severe impairment of the peripheral circulation, the circulation time as measured by the gluside method was only twenty-one seconds, representing a retardation of but slight degree.

A number of similar observations have revealed that in most instances in which the clinical picture of myocardial infarction is dominated by the phenomena of shock, the circulation time as estimated by the gluside method is but little prolonged. Indeed, in case 9, the circulation time was well within the limits of normal. Relatively slight prolongation of the circulation time occurs especially when the infarction is the first from which the patient has suffered and has not been preceded by a period of myocardial insufficiency due to arteriosclerotic disease of the heart. The explanation of the seeming incongruity between the only slightly retarded time as measured by gluside and the clinical picture of obvious and severe circulatory failure lies in the nature of the latter and of the method. It was mentioned previously that the gluside method (as well as other clinical methods for determining circulation time) is largely a measure of the pulmonary circulation time, i. e., of the velocity of blood flow through the lungs. In shock, as will be discussed later, the disturbance of blood flow is largely or exclusively in the periphery of the greater circulation, and it is this primarily peripheral disturbance that produces the coldness and cyanosis of the extremities and the low venous pressure. The comparatively slight prolongation of the time as estimated by the gluside method demonstrates the important fact that in cases of myocardial infarction with the clinical picture of shock, the peripheral circulatory disturbance is accompanied by little or no slowing of the blood flow through the lungs.

On the other hand the circulation time as estimated by the gluside method is prolonged in cases of myocardial infarction which present such symptoms of heart failure as orthopnea, engorgement of the veins and swelling of the liver. Circulation time as slow as thirty or forty seconds, or even more, is common (tables 1 and 3). Prolongation of the circulation time is apt to be especially marked when the infarction has

been preceded by a period of cardiac insufficiency due to coronary arteriosclerosis, and often also hypertension. These patients generally have large hearts, testifying to the antecedent stage of heart failure. Examination also reveals evidence of pulmonary engorgement, and the prolongation of the circulation time is doubtless to be attributed almost entirely to the slowing of the blood flow through the lungs.

VOLUME OF CIRCULATING BLOOD

The volume of the circulating blood was determined in twenty-nine of the patients, in some on two occasions. Table 4 shows the results of the first measurements.

The fact that the volume of circulating blood varies within such wide limits in both directions—the lowest reading 49 cc and the highest 127 cc per kilogram of body weight—indicates that opposing influences come to play on this circulatory variable in myocardial infarction. One factor that we have been unable to gauge is that of abnormality of the volume

TABLE 4—*Volume of Circulating Blood in Myocardial Infarction*

Volume of Circulating Blood, cc of Blood / Kg Body Weight	Cases	Deaths
Less than 70	4	1
70 to 95 (normal)	11	5
More than 95	14	7

of the circulating blood prior to the infarction. In some instances of essential hypertension and of pulmonary emphysema, the volume is increased. As many of our patients had essential hypertension and some were moderately emphysematous, this factor must be taken into consideration in interpreting the volume of blood in rapid circulation. Myocardial infarction is not uncommon in polycythemia vera, but there was no evidence that any of our cases were of this variety.

Comparison of the volume of circulating blood with the rest of the clinical picture in myocardial infarction indicates that two opposing influences are of prime significance in determining the volume of blood in rapid circulation.

1. One of these is the presence of shock, which tends to be associated with a low volume of circulating blood. In initial attacks of myocardial infarction, in which the clinical picture is predominantly that of shock, the volume is subnormal or at the lower limit of the normal range. As the patient recovers from the shock, the volume rises. This was well illustrated in case 14. When the patient first entered the hospital in typical shock due to myocardial infarction, the volume of circulating blood was only 49 cc per kilogram. Ten days later, when the manifestations of shock had largely cleared up, the volume of circulating blood had risen to 73 cc.

2 In cases in which the picture is predominantly that of cardiac failure, the volume of circulating blood tends to be high. It is known that elevation in the volume is common in heart failure, being perhaps a compensatory mechanism. In accord with this, we found that a very high volume of circulating blood (127 cc per kilogram in case 49 and 120 cc in cases 57 and 58) occurred in patients who had had a protracted period of marked cardiac insufficiency prior to the infarction. Presumably, in such patients the elevation in volume persists and is even augmented after the acute phase of the myocardial infarction has been survived, if, as is usually the case, the heart continues to be inadequate. This we found to be true in several of our patients.

It is of special interest that in patients with antecedent heart failure, as well as in others with essential hypertension, infarction may be accompanied by an abnormally high volume of circulating blood, although the clinical features are those of shock. In such patients the venous pressure may be low despite the high volume (cases 49 and 33). These observations show that a subnormal volume of circulating blood is not an invariable characteristic of shock in myocardial infarction.

ARTERIAL PRESSURE

It has long been known that myocardial infarction most often results in a sharp drop in both systolic and diastolic pressure. Indeed, this is so characteristic that when a sudden fall in blood pressure accompanies the onset of circulatory failure in an arteriosclerotic or hypertensive person, the first suspicion entertained is that myocardial infarction has occurred.

The depressor effect of myocardial infarction was of course evident in our series. However, there are exceptional cases in which even elevated blood pressure remains at the previous level despite myocardial infarction with otherwise characteristic clinical features.

Two mechanisms come into consideration as primary pathogenetic factors in the drop in blood pressure accompanying myocardial infarction: (1) heart failure, i. e., decrease in the output of the left ventricle resulting from cardiac weakness and occurring despite adequate venous return to the heart, and (2) the peripheral circulatory failure of shock with consequent diminution in the venous return to the heart.

Comparison of the arterial pressure with the rest of the clinical picture indicates that the second of these mechanisms is generally the more important in causing the fall in arterial tension. In the instances of myocardial infarction in which the clinical features are predominantly those of cardiac insufficiency with intense pulmonary engorgement, the blood pressure tends to be maintained at a level relatively close to that prevailing prior to the infarction. Indeed, as has so often been observed by others under different circumstances, the blood pressure may actually

rise for a time when failure of the left ventricle is severe enough to produce outspoken pulmonary edema. Presumably, this is largely a consequence of asphyxia, being accompanied by intense cyanosis and dyspnea.

On the other hand, the fall in blood pressure is usually pronounced in the episodes of myocardial infarction which are marked by shock and in which the low venous pressure testifies to the deficient venous return to the heart. In such patients, the arterial pressure tends to rise as the other manifestations of shock clear up. However, as is well known, the blood pressure often remains permanently at a lower level than before the infarction. This is presumably due to a persistence of at least part of the cardiac element in the depression of the blood pressure, and is especially apt to occur in cases in which aneurysm of the ventricle develops.

It seems, indeed, that the concomitant presence of shock explains the aforementioned fact that the arterial pressure in many instances of myocardial infarction falls much more than in cardiac insufficiency of other causation. When the heart fails in valvular disease, for example, the only factor tending to depress the arterial pressure is the diminished output of the heart. But physiologic experiments (Tigerstedt¹⁰) show that the arterial pressure is maintained at its previous level by means of peripheral vasoconstriction despite even considerable decrease in the minute volume of the heart. Apparently such a regulatory mechanism functions when the cardiac output is diminished in valvular disease, for the blood pressure rarely falls to any considerable extent, if at all, even though dyspnea, venous and hepatic engorgement and edema evince the insufficiency of the heart. But the situation is different in myocardial infarction with shock. Here, the damage to the heart is accompanied by a functional disturbance in the peripheral circulation, which interferes with regulatory vasoconstriction. Moreover, the peripheral circulatory failure results in diminution in the venous return to the heart, as revealed by the empty peripheral veins and low venous pressure which is so characteristic of the condition. This diminution in venous return to the heart must result in a corresponding decrease in the cardiac output which, in the absence of peripheral vasoconstriction, depresses the arterial pressure.

PERIPHERAL CIRCULATORY FAILURE (SHOCK)

In all our cases of massive myocardial infarction, shock has been at least a significant and often the outstanding feature of the clinical picture. The word "shock" is used in the familiar, strictly clinical sense. The circulatory manifestations of severe shock in myocardial infarction

¹⁰ Tigerstedt, R. *Physiologie des Kreislaufes*, ed 2, Berlin, W. de Gruyter & Co, 1922, vol 3, p 96

are, briefly, the following grayish acrocyanosis, often accompanied by mottling of the skin (*cutis marmorata*) of other parts, notably the abdomen, extremities which are cold in comparison to the rectal temperature, although the actual temperature may not seem low if there is fever, moist skin which generally feels clammy because of the relatively low temperature at the surface, superficial respiration which may or may not be rapid, but no orthopnea, collapsed superficial veins, and a pulse which is most often rapid, small and of low tension

Obviously, this picture is fundamentally identical with the shock which is common following trauma, hemorrhage or the perforation of a viscus. It is also akin to the circulatory collapse of diabetic coma, the crises of Addison's disease and those of various infections, and as such is to be classified as belonging to what Atchley¹¹ aptly termed "medical shock"

It is characteristic of the circulatory failure of shock that it results from disturbances initiated in the periphery of the circulation and not primarily as a consequence of cardiac insufficiency. The nature of the underlying peripheral circulatory disturbances is largely obscure, and doubtless varies in different forms of shock. However, they have as a common consequence, as has long been maintained by Yandell Henderson,¹² a diminution in the venous return to the heart. This is so characteristic, and so diametrically opposed to the venous engorgement of heart failure, that the demonstration of a diminution in venous return to the heart can be taken as adequate evidence that a given instance of circulatory failure is of peripheral origin and not due to insufficiency of the heart.

In the patients with myocardial infarction presenting the clinical picture just described, the existence of peripheral circulatory failure with deficient venous return to the heart is immediately indicated by observation of the superficial veins of the extremities and neck. These appear collapsed and fill slowly when compressed or when the hand is lowered below the level of the heart. When venesection is attempted the blood drips slowly from even a large needle, and to remove any considerable quantity of blood takes a long time. More precise information is afforded by the direct measurements of venous pressure, described earlier, which show that the venous pressure is subnormal. This is all the more significant because it is present despite a severe lesion of the heart which of itself would tend to raise the venous pressure. We have also observed that pressure on the right upper quadrant, which immediately raises the venous pressure in persons with cardiac insufficiency,

11 Atchley, D. Medical Shock, *J. A. M. A.* 95:385 (Aug. 9) 1930.

12 Henderson, Y. Volume of Circulation and Its Regulation by Venopressor Mechanism, *J. A. M. A.* 97:1265 (Oct. 31) 1931.

has no such effect in patients with myocardial infarction and low venous pressure—a further indication of the poor filling of the large veins

The observations made furnish no unequivocal evidence regarding the causation of the low venous pressure in myocardial infarction. The problem is really only one aspect of the fundamental question of the origin of circulatory shock in general, which is still *sub judice*. Investigations of recent years (Atchley¹¹) have shown that diminution in the volume of circulating blood is an important factor in many forms of shock, and that therapeutic measures which increase the volume often have a salutary influence on shock. The measurements described earlier show that in myocardial infarction the volume of circulating blood tends to be lowered, and in some of the cases is much below normal. However, it was also mentioned that in other cases with the typical picture of shock, including low venous pressure, the volume is normal or above normal. It seems probable that in these patients, as a result of cardiac failure or in correlation with hypertension, the volume of circulating blood was even higher prior to the infarction. The possibility, therefore, must be borne in mind that in such cases there may be a relative decrease in the volume of circulating blood below that to which the capacity of the vessels has become adjusted. The mechanism of the fall in the volume of circulating blood remains to be elucidated. We found no constant abnormality in the hematocrit reading or in the red blood cell count, which shows that extravasation of the plasma, so important in other forms of shock, plays no considerable part in that of myocardial infarction. It is therefore to be presumed that the diminution in the volume of circulating blood is due to a redistribution of the blood, whereby a smaller fraction of the total volume of blood in the body remains in active circulation and a larger fraction is stagnated in dilated capillaries and perhaps within the blood depots, originally described by Barcroft,¹³ where it is not reached by the dye injected and contributes little to the venous return to the heart.

How myocardial infarction leads to the disturbances in the peripheral circulation, one of the manifestations of which is a decrease in the volume of the circulating blood, is another question to which we are unable to give an adequate answer. A chemical mechanism, with liberation from the necrotic heart muscle of substances with histamine-like action, seems improbable, because the shock and low venous pressure may set in within a short period after the onset of the first symptoms, before actual necrosis could be considerable. A nervous mechanism would seem much more likely. That reflexes actually affect the peripheral circulation in

13 Barcroft, J, and others. Observations upon the Effect of Altitude on the Physiological Processes of the Human Body, Tr Roy Soc, London, s B 211 351, 1922

14 This footnote was deleted by the author

coronary occlusion was indicated by Condorelli,¹⁵ who found that occlusion of the left coronary artery of a dog is followed immediately by a considerable fall in the aortic pressure, which rises as soon as the coronary clamp is released, but if he cut the vagus and sympathetic nerves on both sides, subsequent occlusion of the left coronary artery caused no notable depression of the aortic pressure until ventricular fibrillation set in. How such reflexes affecting the peripheral circulation are initiated in myocardial infarction is unknown. It is not the anginal pain that set the mechanism in operation, for shock may be severe in myocardial infarction in the absence of pain. Indeed, Libman¹⁶ found that shock is apt to be especially pronounced when myocardial infarction affects hyposensitive persons who do not complain of pain.

HEART FAILURE IN MYOCARDIAL INFARCTION

In other patients with myocardial infarction, usually those with a history of severe heart failure or prior infarctions, the symptoms are largely those of cardiac insufficiency. Evidence of failure of the left ventricle with pulmonary engorgement is always present, sometimes alone and sometimes combined with insufficiency of the right side of the heart, as manifested by a rise in the venous pressure and swelling of the liver. Peripheral edema, however, is unusual, it was present in but five of our fifty-nine cases. The circumstances under which failure of the right side of the heart was observed have already been discussed in conjunction with high venous pressure. In the cases showing the clinical picture of heart failure, the circulation time was prolonged and the volume of circulating blood increased.

Isolated failure of the left side of the heart is not infrequent in myocardial infarction. Most often, it is due to anterior infarction of the heart consequent on thrombosis of a branch of the left coronary artery. However, it may also result from posterior infarction in right coronary occlusion. The outstanding circulatory symptoms are dyspnea and orthopnea with evidence of pulmonary engorgement and accentuation of the second sound at the pulmonic area. The venous pressure is not elevated, and the liver is not enlarged. The pulmonary circulation time is prolonged, usually strikingly so. Episodes of paroxysmal nocturnal dyspnea are common. We have seen such banal symptoms of failure of the left ventricle in hypertensive and arteriosclerotic subjects, in whom only the electrocardiogram revealed that recent infarction was responsible. The extreme form of failure of the left ventricle

15 Condorelli, L. *Die Ernährung des Herzens und die Folgen ihrer Störung*, Dresden, Theodor Steinkopff, 1932, p. 67.

16 Libman, E. *Studies in Pain*, *Tr. A. Am. Physicians* **34**: 52, 1929.

in myocardial infarction is that in which massive pulmonary edema develops, which may lead to quick death

Pletnew,¹⁷ Kohan and Budin¹⁸ and others thought that they were able to infer the site of coronary thrombosis from the type of heart failure present. They reported observations indicating that thrombosis of the left coronary artery with anterior infarction results in failure of the left ventricle with pulmonary engorgement and enlargement of the heart to the left. On the other hand, they found that thrombosis of the right coronary artery with posterior infarction is characterized by failure of the right side of the heart, with swelling of the veins and liver and enlargement of the heart to the right. We have not found such a differentiation feasible. Our necropsy observations revealed that either anterior or posterior infarction can cause isolated failure of the left ventricle or combined insufficiency of the left and right ventricle with engorgement of both the lungs and the systemic veins. And when shock dominates, the venous pressure is low in thrombosis of the right as well as of the left coronary artery. Because of these observations, it has not seemed that the type of circulatory failure present permits, of itself, the differentiation between right and left coronary occlusion. However, Libman¹⁹ found that when the liver becomes greatly enlarged within a few hours after the onset of myocardial infarction, the right coronary artery is the one affected.

In those of our patients with severe failure of the right side of the heart and high venous pressure who came to necropsy, extensive infarction of the interventricular septum was present. Such septal infarction may be due to thrombosis of either the right or the left coronary artery. Whether high venous pressure in coronary thrombosis is always due to septal infarction must be studied on more extensive material. However, it must be emphasized that even with extensive septal infarction the venous pressure in coronary thrombosis is low if shock dominates, the clinical picture.

INTERRELATIONS OF SHOCK AND HEART FAILURE

The foregoing observations indicate that in myocardial infarction two distinct mechanisms operate to derange the circulation: (1) cardiac insufficiency, which tends to produce engorgement and a rise in pressure in the pulmonary circuit and in the systemic veins, and (2) shock, which

17 Pletnew, D. Zur Frage der intravitalen Differentialdiagnose der rechten und linken Coronarthrombose des Herzens, *Ztschr f klin Med* **102** 295, 1925

18 Kohan, B. A., and Budin, E. I. Zur Frage der Differentialdiagnose der rechten und der linken Koronararterie des Herzens am Lebenden, *Ztschr f Kreislaufforsch* **20** 199 (April 1) 1928

19 Libman, E. Some Observations on Thrombosis of the Coronary Arteries, *Tr A Am Physicians* **34** 138, 1919

diminishes the venous return to the heart and thereby tends to deplete and lower the pressure in the pulmonary circuit and great veins

As regards the minute volume of the heart, both these derangements are synergistic, each tending to diminish the cardiac output. On the other hand, the two derangements are antagonistic in their effect on the venous pressure, heart failure tending to raise it and shock to lower it. The observation of the veins and the measurement of the venous pressure thus furnish a valuable index of the relative significance of shock and of cardiac insufficiency in producing circulatory failure in a patient with myocardial infarction. That this is a point with important therapeutic implications is evident.

As indicated in the section on venous pressure, the clinical picture of initial myocardial infarction is most often predominantly that of shock. Indeed, symptoms of heart failure may be entirely lacking despite clinical and electrocardiographic evidence of extensive infarction. The explanation of this remarkable phenomenon would seem to be that the presence of shock militates against the development of heart failure through the following mechanisms:

1. Symptoms of heart failure appear when the work which the heart is called on to perform exceeds the functional capacity of a chamber, so that it fails to empty as completely as before, and engorgement develops up-stream to the insufficient chamber. The work of the heart is a function of the volume of blood it is called on to pump (i. e., the venous return) and the resistance against which the blood has to be pumped (i. e., the pulmonary and aortic arterial pressures). In shock, both these factors are subnormal, for the venous return to the heart is decreased and the arterial pressure is depressed.

2. The decrease in the work of the heart due to shock in myocardial infarction may be so great that even the severely damaged heart is able to pump the smaller volume of blood that returns to it against the lowered aortic pressure. In such cases the circulatory status is that of shock, and evidence of heart failure is absent. In other instances, on the contrary, the diminution in the work of the heart is not sufficient to bring it within the functional capacity of the infarcted organ. In this event, orthopnea, signs of pulmonary engorgement, high venous pressure, swelling of the liver or other signs of heart failure develop. But even in such instances, the concomitant presence of primarily peripheral disturbances in circulation is often indicated by such manifestations as coldness and cyanosis of the hands disproportionate to the other evidences of heart failure, moisture of the skin and cutis marmorata.

A not uncommon sequence of events is the following. In the first days after the infarction, the clinical picture is that of shock with low venous pressure. Subsequently, most often between the second and

tenth days, the shock clears up and evidences of heart failure appear in the form of orthopnea and signs of pulmonary engorgement, with an accompanying rise in venous pressure. It is at this period that evidences of bronchopneumonia most often appear, they are perhaps correlated with the increasing pulmonary engorgement as the venous return to the heart increases before the left ventricle has recuperated sufficiently to master it.

In a real sense, then, shock operates as a protective mechanism for the heart in myocardial infarction. Of course, it is protection bought at a high price, for some patients succumb with the typical manifestations of shock. And the decreased cardiac output with low aortic pressure presumably lessens the coronary flow, which may be concerned in the production of ventricular fibrillation. But in other cases it may be presumed that the heart would not be able to carry on its function were it not for the decreased cardiac work due to shock. Moreover, the diminished work of the heart in shock must be accompanied by lower maximum intraventricular tension, and this may be an important reason why rupture of the heart occurs in only a small minority of instances of even extensive myocardial infarction. It is probably also the explanation of the fact that enlargement of the heart over its antecedent dimensions is most often not demonstrable in the first days of myocardial infarction.

In our cases of myocardial infarction, the immediate prognosis has been statistically much better when the clinical picture was that of shock with low venous pressure than when there was heart failure with high venous pressure. Of nineteen patients with venous pressure below 4 cm on admission, five died. On the other hand, of nineteen patients who entered the hospital with venous pressure above normal, fifteen died. Of course, this difference is probably largely correlated with the fact, brought out previously, that low venous pressure is more common in initial infarction, while high venous pressure usually occurs in those with previous severe functional impairment of the heart. For the same reason, the prognosis is statistically much worse when the circulation time is greatly retarded (table 3).

THERAPY

It is not our purpose to discuss therapy. However, it may be pointed out that in myocardial infarction with shock and low venous pressure, as the patient at the time is not suffering from cardiac insufficiency, there would seem to be no indication for digitalis. Presumably, the general ill-repute of digitalis in myocardial infarction originated in its lack of beneficial effect in such cases. Venesection is also out of place, and is rendered difficult by the low pressure in the superficial veins. On the other hand, venesection and digitalis may be of great service in cases in which there is heart failure with pulmonary and venous engorgement.

The value of digitalis for such patients is often demonstrated objectively by the rapid fall in venous pressure to normal levels following digitalization. However, it should be borne in mind that, at least theoretically, digitalis predisposes to certain dangers in myocardial infarction. Notable among these are ventricular fibrillation as a result of greater irritability of the heart muscle, rupture of the heart or embolization of intraventricular thrombi in consequence of a more powerful systole, and possible deleterious effects of the coronary constriction as demonstrated by Gilbert and Fenn²⁰. Whether these dangers are actual can be established only by observation of a larger series of cases. In any event, it seems obvious that the type of circulatory failure present should be taken into account in the treatment of myocardial infarction.

SUMMARY

Fifty-nine patients with recent myocardial infarction were studied from the point of view of circulatory dynamics. The venous pressure was measured in all, the circulation time in thirty-eight and the volume of circulating blood in twenty-nine of the subjects.

Two distinct mechanisms participate in the derangement of the circulation in myocardial infarction. (*a*) shock, or peripheral circulatory failure, which diminishes the venous return to the heart and tends to lower the pressure in the large systemic veins, and (*b*) heart failure, which tends to engorge the pulmonary circuit in consequence of insufficiency of the left side of the heart and to raise the systemic venous pressure in proportion to the insufficiency of the right side of the heart.

In initial myocardial infarction in persons without previous severe heart failure, the clinical picture is most often predominantly that of shock. The venous pressure is then subnormal. The blood flow through the lungs is slowed but little, if at all. The volume of circulating blood tends to be diminished.

When infarction affects patients with previous heart failure, the manifestations of either shock or cardiac insufficiency may be predominant. When heart failure dominates, the venous pressure is elevated or normal, the flow of blood through the lungs is retarded, and the volume of circulating blood is increased.

The diminished venous return due to shock lessens the work of the heart and thus militates against the development of cardiac insufficiency. It is because of this diminution in the venous return to the heart that engorgement of the lungs and systemic veins may be absent despite extensive myocardial infarction.

²⁰ Gilbert, N. C., and Fenn, G. K. The Effect of Digitalis on Coronary Flow, *Arch Int Med* 50:668 (Nov.) 1932.

The fall in arterial pressure is due not only to the weakness of the left ventricle but also to the peripheral circulatory failure of shock. Apparently the latter is usually the more important of the two factors. It is because of the concomitant presence of shock that a fall in the arterial pressure is so much more prominent in myocardial infarction than in other lesions of the heart.

Statistically, the immediate prognosis of myocardial infarction is better with low than with high venous pressure.

The type of circulatory failure present is of significance for the rational treatment of patients with myocardial infarction.

News and Comment

INTERNATIONAL CONGRESS OF GASTRO-ENTEROLOGY

The First Congress of Gastro-Enterology will be held at Brussels, Belgium, Aug 8 to 10, 1935. The secretary-general of the Congress is Dr. George Brohee, Rue de la Concorde, 64, Brussels. Dr. Max Einhorn, 20 East 63rd Street, New York, has been asked to form and to act as chairman of, the North American Committee, and Dr. De Witt Stetten to serve as secretary of the committee.

Book Reviews

A Textbook of Bacteriology By Hans Zinsser, Professor of Bacteriology and Immunology, Harvard University Medical School, and Stanhope Bayne-Jones, Professor of Bacteriology, Yale University Medical School Price, \$8 Pp 1,226, with 174 illustrations New York D Appleton-Century Company, 1934

In 1910, Philip H Hiss Jr and Hans Zinsser published the first edition of their textbook of bacteriology As they stated, the book was primarily a treatise on the fundamental laws and technic of this science, it was written in the hope of meeting the bacteriologic needs of medical students and also to interest practitioners in a fascinating subject The book at once became recognized all over the world and soon earned a well deserved popularity, so that subsequent editions were published in 1914, 1916, 1918, 1922, 1927 and 1934

The 1934 edition lives up to the standards of its predecessors It brings the subject matter up to date, it is easily readable, being written in delightfully clear and succinct English, and it is printed in type comfortable to the eye and is well illustrated At the end of each chapter are a few good references to the topics under discussion, thus prompting even the most casual student to further knowledge, and at the end of the book is an excellent index

Bacteriology appears to be an extraordinarily alive subject The second edition of this textbook, published twenty years ago, described adequately current knowledge of the subject A volume nearly twice as large is necessary to accomplish the same purpose today As one compares the second edition with the seventh, one is struck with the pertinency of what the authors remark in their preface to the latest edition Certainly, the last few years have been eventful ones in bacteriology, and some of the newer knowledge has been revolutionary in its effect on old theories The book is so written as to take due cognizance of this It also lays more emphasis than heretofore on the diseases caused by Rickettsia and on the ultramicroscopic virus agents

On the whole, this textbook deserves highest praise Without doubt, it will fulfil the purpose for which it was written and will prove useful to bacteriologists, physicians and all those who are engaged in the investigation, management and prevention of infectious disease

The Lyophilic Colloids (Their Theory and Practice) By Martin H Fischer and Marian O Hooker Price \$4.50 Pp 246, with 84 illustrations Springfield, Ill Charles C Thomas, Publisher, 1933

This volume is a resume of the work done by these two capable scientists during the last ten years not only in developing their concept of the physical state of matter (protoplasm) but also in studying the physical and chemical laws which make this concept probable By studying the physical and physicochemical properties of such colloidal systems as phenol/water, quinoline/water and casein/water (to mention a few), they arrived at the conclusion that protoplasm itself is not a solution of protein and minerals in water, but that it is actually one of the inverse type In other words, instead of being a dilute solution of "X" in water, it is a concentrated solution of water in "X," and as such cannot possibly fit into the schemata proposed by the "dilute solution" chemists As a corollary to the axiom may be mentioned new and extremely interesting information regarding the disfranchisement of the cell membrane and the osmotic theory, as well as the proposal of new explanations for such phenomena as the absorption of water, edema, the relation of electrolytes, protein and water in the cell, acidosis and alkalosis, and, finally, synthesis within the cell itself

The physician will be most interested in the third portion of the book, which deals with biologic applications, but in order to attain properly the authors' point of view it is necessary to read carefully part one, which reveals the general nature of the lyophilic colloid. Part two, on chemical applications, will not prove of much interest to students of medical science.

The volume is clearly written, and the arguments are logically presented, but a more orderly arrangement of the many illustrations and graphs with reference to the context would not be amiss. It might be added that the reader who has no previous knowledge of the colloidal state will probably find himself somewhat handicapped in attempting an intelligent and complete understanding of the work.

Traité de physiologie normale et pathologique Tome V Respiration
Published under the direction of G. H. Roger and Léon Binet. Price, 80 francs, stitched, 100 francs, bound. Pp 474, with 147 figures and 3 colored plates. Paris: Masson & Cie, 1934.

This volume is the fifth of a work of eleven volumes on normal and pathologic physiology. A general preface points out that a treatise of this sort, while emphasizing the value of facts in the development of the present position of a science, should also point out the imperfections and the unfinished nature of the knowledge.

The work purports, in spite of its size, to be merely elementary, treating only of what is indispensable to a solid foundation of pathology.

The subdivisions of the subject "Respiration" have, as in the other volumes of the work, been written by various authors, as follows: "The General Principles of Tissue Respiration," by P. Thomas, "The Histophysiology and Biochemistry of the Lungs, and Pulmonary Ventilation" (mechanics, pulmonary circulation, comparative physiology and the pleura, by L. Binet, a long and interesting chapter, "Gaseous Exchange," by L. Dautrebande, "The Internal Functions of the Lungs, Exclusive of Gaseous Exchange" (the influence on blood fat, cholesterol, lecithin, antitoxic action, coagulation of the blood, etc.), also by L. Binet, and a chapter "Basal Metabolism" by H. Hermann. Another particularly interesting chapter is "The Nervous Control of Respiration," by C. Heymans, who is preeminently capable of discussing this matter. Binet has also written a chapter "Abnormal Breathing" (asphyxia, mountain sickness, excess of oxygen, oxygen and carbon dioxide treatment of asphyxia, artificial respiration, drugs stimulating the respiratory center and other phases of the subject).

The work is a credit to the French and Belgian authors who have collaborated in producing this volume. The foreign modern literature is well represented in the references.

Médecine et éducation By Drs G. Mouriquand, M. Pehu, P. Bertoye, J. Barbier, P. Vignard, P. Mazel and P. D'Espiney, Father R. P. Charmot and Abbot J. Monchanin. Price, 15 francs, 50 centimes. Pp 224. Lyon: Lavandier, 1934.

In Lyon a group of doctors, philosophers and biologists have evidently grouped together to study various complexities of human life. The first volume of their publications dealt with matters pertaining to sex, the second with heredity and the third with the importance of rhythm to life. The fourth was entitled "Formes, vie et pensée." The present volume deals with education.

This volume is a compilation of essays by the various authors of the book, showing in general that for the benefit of posterity the physician must play an increasingly important part in the process of education and must bring to bear the light of his special knowledge on the problems which perplex school teachers. Each chapter is interestingly written, beginning with an introductory appeal to educators for the collaboration of physicians by Father Charmot and ending with a concluding chapter on the ideals of education by Abbot Monchanin. The body

of the book is written by a group of physicians who discuss such topics as the physical and mental development of children, conditional reflexes and their rôle in education, the importance of adequate physical education to mental development, sex education and methods of handling nervous children or children with antisocial tendencies

The book is an unusual one and should prove stimulating to physicians in this country who are school physicians or who are concerned with the management of young patients. On the whole, it is worth reading.

Die klinische Röntgendiagnostik der inneren Erkrankungen By Dr Herbert Assmann. Fifth edition. Price, 87 marks. Pp 1248. Berlin F C W Vogel, 1934.

Assmann's book, which is familiar to every radiologist and internist, may now be said to have become a classic, "monumental" is the only adjective which adequately describes this vast compendium. The reviewer obviously can single out only a few points for comment. First, the general get-up—paper, printing and arrangement—is excellent and of a sort appropriate for a durable book, the work is conveniently divided into two volumes. Next should be mentioned the diagrams and reproductions of roentgenograms, more than 1,200 in number, illustrating every phase of the subject. Not only are these illustrations well selected, but the technical reproduction is excellent. The text, on the whole, is sound and is clearly written by one familiar with both the roentgenologic and clinical aspects of internal diseases. Reports of individual cases of typical, rare and interesting conditions make it possible for the physician to orient himself on practically any problem which he may encounter. That the revision is up to date is shown by the inclusion of such topics as arteriography. The bibliographies appended to each section are comprehensive, and there is an index. A particularly useful feature is the discussion of the normal roentgenologic appearances of the various organs—the heart, gastrointestinal tract and others.

Clinical Miscellany The Mary Imogene Bassett Hospital, Cooperstown, N Y. Volume I. By several contributors. Price, \$3. Pp 206, with 15 illustrations, 25 charts and graphs and index. Springfield, Ill. Charles C Thomas, Publisher, 1934.

Twenty-two articles by eight members of the hospital staff on a "collection of selected clinical observations with interpretative comments" representing "an effort to activate fragments of experience" comprise the volume. Each case is clearly presented and has been thoroughly studied. Most commendable is the scientific curiosity evidenced in the "interpretative comments."

With the literature so crowded and with such easy access to standard medical publications, one questions the advisability of publishing such a collection, apparently the first of a series of which this is volume 1. The book is printed on good paper and is well bound, and the illustrations are excellent.

Handbook of Therapeutics By David Campbell. Second edition. Price, \$4.75. Pp 444, with 72 figures and 9 tables. Baltimore, William Wood & Company, 1934.

This little book gives in fairly adequate form the treatment of internal disease. Like all brief compendia it suffers in places from undue abbreviation, as well as from the inclusion of some material which is relatively useless, such as brief remarks on climatotherapy, spas, etc. The point of view, on the whole, seems sound, with some glaring lapses, for example the suggestion that a few brief courses of therapy intermittently given suffice in the early stages of syphilis. A great many statements, such as the dietary prescriptions for Bright's disease, do not seem to rest on any rational basis. On the whole, the book is satisfactory, but a really adequate brief outline of therapy remains to be written.

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